VALIDATION OF THE MODIFIED VACS INDEX IN A HIV INFECTED SOUTH INDIAN POPULATION INITIATED ON A NACO - ART REGIMEN: A COHORT STUDY

A Dissertation submitted in partial fulfilment of the

M.D (General Medicine) branch I Examination of the Tamil Nadu

Dr. M.G.R. UNIVERSITY, CHENNAI

to be held in 2016

DECLARATION

This is to declare that this dissertation titled "**VALIDATION OF THE MODIFIED VACS INDEX IN A HIV INFECTED SOUTH INDIAN POPULATION INITIATED ON A NACO - ART REGIMEN: A COHORT STUDY"** is my original work done in partial fulfilment of rules and regulations for MD General Medicine examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2016.

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CERTIFICATE

This is to certify that the dissertation entitled, "**VALIDATION OF THE MODIFIED VACS INDEX IN A HIV INFECTED SOUTH INDIAN POPULATION INITIATED ON A NACO - ART REGIMEN: A COHORT STUDY**" is a bonafide work done by Dr. Aditya John Binu towards the partial fulfilment of rules and regulations for MD General Medicine degree examination of the Tamil Nadu Dr. M.G.R Medical University, to be conducted in April 2016.

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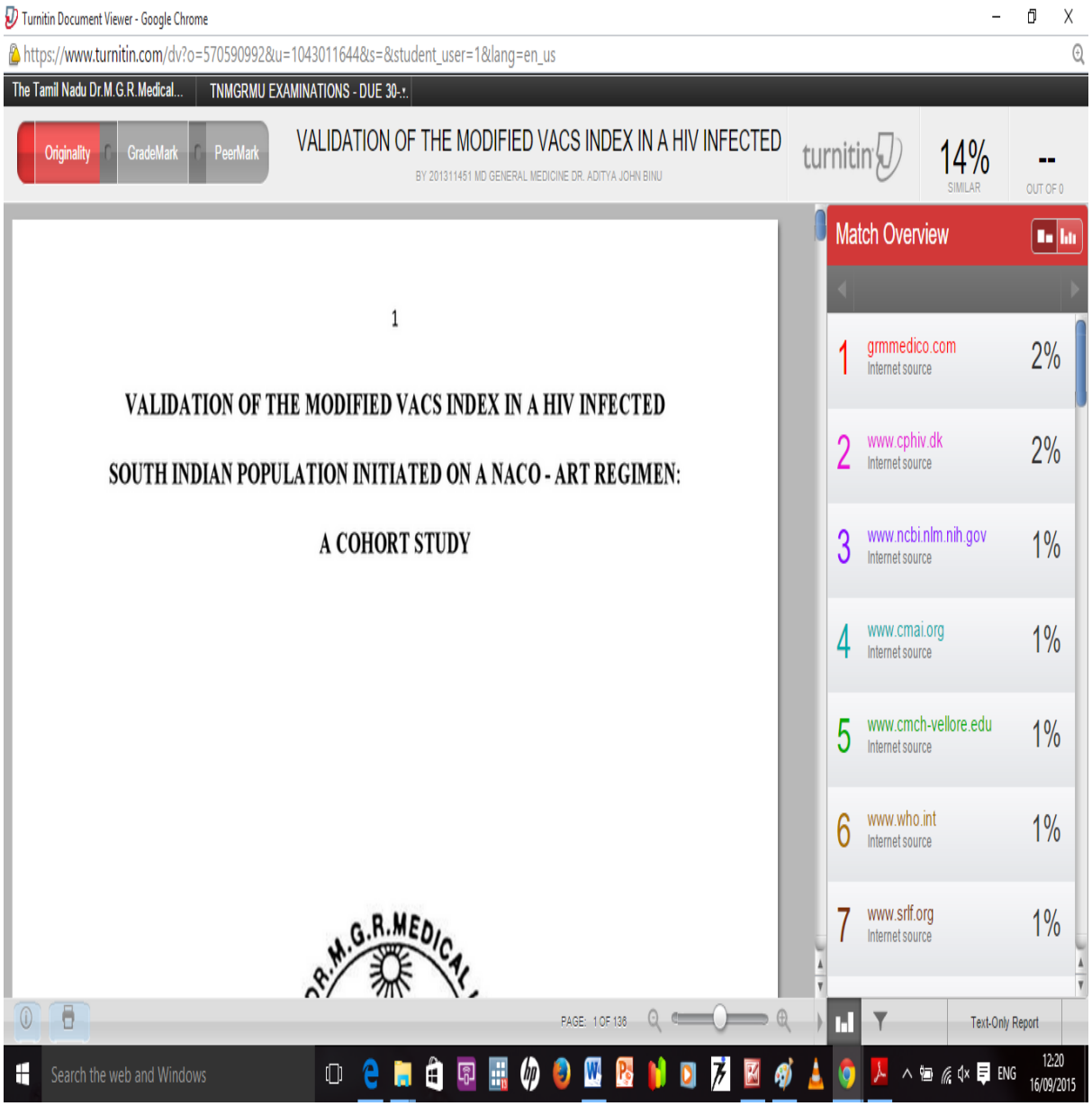
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At the outset, I thank my guide Dr. O. C. Abraham with all my heart for meticulously and painstakingly guiding me through the entire process of completing my dissertation. I am equally grateful to my senior co - guide and the Head of the Department of Medicine Dr. Anand Zachariah. I was fortunate to benefit from the wealth of their knowledge and expertise. I cannot thank them enough for all the patience and kindness with which they dealt with me and every single problem that I had during this course. I would also like to thank my junior co-guide Dr. Sam P. Mannam for his astute and timely observations.

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Sub: **Fluid Research grant project:**
Validation of the modified VACS index in a south Indian population with HIV infection and on initial ART regimen under the NACO Programme: A Cohort study.
Dr. Aditya John Binu, PG Registrar, General Medicine, Dr. O.C. Abraham, Medicine, Dr. Sam Prasad Mannam, General Medicine.

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Dear Dr. Aditya John Binu,

I enclose the following documents:- 1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
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Institutional Review Board

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Dear Dr. Aditya John Binu,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Validation of the modified VACS index in a south Indian population with HIV infection and on initial ART regimen under the NACO Programme: A Cohort study." on November 12th 2013.

The Committees reviewed the following documents:

1) IRB application format
2) Curriculum Vitae' of Dr. Aditya John Binu, Dr. O.C. Abraham, Dr. Sam Prasad Mannam
3) Information Sheet (English, Hindi & Tamil)
4) Consent form (English, Hindi & Tamil)
5) Clinical Research Form
6) No of documents 1-5

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The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on November 12th 2013 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. Simon Rajaratnam	MBBS, MD, DNB (Endo), MNAMS (Endo), PhD (Endo), FRACP	Professor, Endocrinology, CMCH.	Internal, Clinician
Dr. T. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMCH.	Internal, Clinician
Dr. Chandra Singh	MS, MCH, DMB	Professor, Urology, CMCH.	Internal, Clinician
Dr. Visalakshi	MPH, PhD	Lecturer, Dept. of Biostatistics, CMC.	Internal, Statistician
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Colorectal Surgery, CMCH.	Internal, Clinician
Dr. Anup Ramachandran	Ph. D	The Wellcome Trust Research Laboratory Gastrointestinal Sciences, CMCH.	Internal, Basic Medical Scientist
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMCH.	Internal, Clinician
Dr. Rajesh Kannangai	MD, Ph D.	Professor & In-charge Retrovirus Laboratory (NRL under NACO), Department of Clinical Virology, CMCH.	Internal, Clinician

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We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 6,300 INR (Rupees Six Thousand Three Hundred only) will be granted for 2 years.

Yours sincerely

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Cc: Dr. O.C. Abraham, Department of Medicine – I, CMC

Table of Contents

1. INTRODUCTION

The World Health Organisation (WHO) has recorded 31.8 million [30.1 million – 33.7 million] adult patients as infected with the Human Immunodeficiency Virus (HIV) with 1.9 million [1.7 million – 2.1 million] people diagnosed for the first time, as per the global summary of the AIDS epidemic (2013).(1) As is evident from these figures, HIV/AIDS still remains a vital global health issue. The National AIDS Control Organisation (NACO) statistics reveal that India has the third highest number of people infected with HIV in the world. The prevalence has been projected to be approximately 20.89 lakh, with 0.27 % in the adult age group (15-49 years) in 2011.(2)

Highly active antiretroviral therapy (HAART) is essential for management of patients with HIV infection. The EuroSIDA study compared the early ART period to pre-ART and later ART treatment periods, and showed a reduced mortality and progression to AIDS on continuous ART. Widespread use of ART has resulted in a marked decline in the incidence of most AIDS defining conditions and mortality both in the developed and developing world.(3) Suppression of HIV replication is essential to prevent HIV associated morbidity and mortality; it also improves the quality of life in patients with HIV infection. Strict adherence to antiretroviral therapy is required for adequate suppression of HIV infection.(3)

ART has been dispensed free of cost under the National AIDS Control Programme (NACP II) since April 2004. More than 300 ART centres are functional in India at present and more than 516,000 patients are receiving ART at these centres. Approximately 30,000 patients receive free ART in the private sector.(4) Consequently, there has been a progressive decline in annual AIDS related mortality with approximately 1,50,000 lives being saved due to ART till 2011.(2)

Despite adequate treatment with ART, excess mortality has been observed in these individuals as compared to matched controls and is not explained by parameters like CD4 count alone. Studies like the SMART trial point towards probable etiologies such as HIV-associated inflammation with increased risk of hypercoagulability and aging-associated organ system injury.(5)There has been an increasing body of evidence suggesting that the risk of serious non-AIDS conditions like cardiovascular disease (CVD), renal or hepatic disease and non-AIDS defining malignancies is increased in people with HIV infection as compared to matched controls.(6) Multiple trials have been conducted to assess correlation of non-traditional with traditional markers of inflammation to monitor patients with potentially modifiable risk factors.

Physicians treating patients with HIV infection are frequently asked for prognostic assessments and quality of life after initiating therapy. Prognostic systems such as risk factors, staging systems, statistical models, and computer algorithms have been developed to standardize and enhance the accuracy of prognostic assessments. The

Veterans Aging Cohort Study (VACS) Risk Index was designed to predict mortality in HIV patients who have been treated for one year, using a simple scoring system. It was intended to take into account all possible effects of HIV disease, comorbidities, substance abuse, and adverse drug reactions secondary to treatment, on outcome in HIV-infected patients.(7)

The basis of our study was to utilise a cost effective modification of the VACS Index – the modified VACS index - and find a significant correlation between the predicted and actual mortality in a cohort of HIV infected patients who had been initiated on anti-retroviral therapy (ART). The index would aid physicians in gauging clinical improvement and the effect of other modifiable factors on the health of PLHIV; it also gives patients an objective measure of chances of mortality in case of non-compliance with treatment and would help in greater adherence to the prescribed ART protocol.

2. AIMS

- To validate the Modified Veterans Ageing Cohort Study (VACS) Index in a South Indian Population infected with the Human Immunodeficiency Virus (HIV) initiated on Anti-Retroviral Therapy (ART).

3. OBJECTIVES

a. To predict patient mortality in HIV infected patients attending the ID clinic who have been started on ART regimen under NACO over a 1 year period from 1st June 2012 to 31st May 2013 and follow up over a 2 year period from 1st June 2013 to 31st May 2015 using the Modified VACS index derived from baseline blood parameters.

b. To compare predicted mortality with actual mortality in the cohort over a 2 year period from 1st June 2013 to 31st May 2015.

c. To use this data to design and implement effective interventions to improve outcomes among patients with HIV infection.

4. LITERATURE REVIEW

4.1 STRUCTURE AND CLASSIFICATION

The human immunodeficiency virus (HIV) has been classified in the family of retroviruses, which is distinct in the fact that their genetic information happens to be encoded by ribonucleic acids (RNA) rather than deoxyribonucleic acids (DNA). They act by infecting and consequently destroying CD4 T- cells. HIV is the aetiological agent of acquired immunodeficiency syndrome (AIDS). HIV is classified into 2 types, both of which are known to cause AIDS: HIV-1, which is the predominant cause of the global epidemic; and HIV-2, which is less pathogenic and mostly restricted to West Africa. Since the identification of the virus almost three decades ago, the pandemic form of HIV-1 has been diagnosed over all continents and countries; the infection also encompasses all age groups. Developing countries have borne the brunt of HIV/AIDS related morbidity and mortality.(8)

HIV-1 comprises of four distinct lineages, which have been classified into groups M, N, O, and P. All four of these groups came into existence secondary to an independent cross-species transmission event. Group M was the first to be recognised and is known as the pandemic form of HIV-1; it is ubiquitous with regards to its geographic distribution. Group O was discovered in 1990 and is much less prevalent than group M (<1% of global HIV-1 infections) and is mostly restricted to Cameroon, Gabon, and neighbouring countries (Mauclere et al. 1997; Peeters et al. 1997). Group N was

identified in 1998 (Simon et al. 1998). It is less prevalent than group O with only 13 cases having been documented, with all the patients hailing from Cameroon (Vallari et al. 2010). Group P was the last to be discovered in 2009; it was detected in a Cameroonian woman living in France (Plantier et al. 2009). Despite extensive screening, group P has thus far only been identified in one other person, also from Cameroon (Vallari et al. 2011). All these groups are known to cause CD4 T-cell destruction and AIDS.

4.2 ROUTES OF TRANSMISSION

HIV-1 is propagated by sexual, percutaneous and perinatal routes; approximately 80% of adults get infected following exposure at mucosal surfaces. AIDS usually occurs after an approximate duration of 6 to 9 years following infection with the virus. AIDS consists of a group of opportunistic infections and other characteristically associated conditions, or malignancies. The spectrum of AIDS occurs as a result of the underlying immunodeficiency. AIDS occurs as a consequence of chronic HIV infection with depletion of CD4 cells.

4.3 ETIOPATHOGENESIS

HIV targets multiple cell lines such as dendritic cells, macrophages, and CD4+ T cells. The most common portal of entry of HIV-1 into a host is through the ano-genital mucosa. The envelope protein of the virus, glycoprotein (GP)-120, binds to the CD4 molecule on dendritic cells. Interstitial dendritic cells in the cervico-vaginal

epithelium as well as tonsillar and adenoidal tissue, may also be the initial target cells in infection transmitted via genital-oral sex. Transmission of macrophage tropic rather than T-cell tropic viruses are more commonly the cause of newly acquired HIV infection. Different co-receptors aid viral entry into cells. GP-120 must bind to the chemokine receptor CCR5 as well as CD4 in order for the virus to enter macrophages,. Macrophage tropic viruses are designated as R5 in comparison to T cell tropic viruses, which are called X4, based upon the CXCR4 receptor on these cells. Patients homozygous for a deletion in CCR5 are relatively resistant to R5 infection, but cases of X4 infection have rarely been reported in these individuals.

HIV infected cells fuse with CD4+ T cells, leading to spread of the virus. HIV is detectable in regional lymph nodes within two days of mucosal exposure and in plasma within another three days. Once virus enters the blood, there is widespread dissemination to organs such as the brain, spleen, and lymph nodes. The intestinal mucosa is also a primary target during initial infection. Preferential destruction occurs in CD4+ memory T cells, which may result from direct infection as well as through apoptosis. This can lead to an early and disproportionate loss of CD4+ T cells in the gastrointestinal compartment, compared to peripheral blood. It has also been proposed that microbial translocation, due to changes in the gut mucosal barrier, may be the etiology of chronic immune activation in HIV infection.

The virus penetrates mucosal epithelium, followed by infection of submucosal CD4+ T cells, dendritic cells, and macrophages with subsequent spread to lymph nodes and ultimately, plasma. Viremia was documented between 5 to 30 days after experimental intravaginal HIV exposure. HIV RNA levels rapidly increase from the earliest quantifiable measure to a peak level that usually coincides with seroconversion. However, a period of low-level viremia preceding ramp-up viremia, may be more common than originally thought. A study of serial samples from patients with confirmed early HIV infection was performed to determine if low levels of viremia were present in samples that were negative by prior quantitative PCR. On retesting with a sensitive qualitative reverse transcriptase PCR assay with sensitivity of 4 copies / mL, 23 of 69 samples were subsequently positive. These specimens preceded the first sample with >100 copies / mL by 9-25 days. Whether blood is infectious at this low level of concentration is not known.

The HIV DNA level in peripheral blood mononuclear cells provides an estimate of the cellular HIV reservoir, which is established soon after infection. In one study of 163 patients who did not start immediate antiretroviral therapy after diagnosis of acute infection, the HIV DNA level and initial CD4 cell count were found to be independent predictors of disease progression.

4.4 CASE DEFINITION

AIDS occurs as a result of chronic HIV infection and a resultant reduction in the number of CD4 cells. A case definition may be stated as a CD4 cell count <200 cells/ µL or the presence of any AIDS-defining condition regardless of the CD4 cell count. The term advanced HIV infection is often used to refer to infection when the CD4 cell count is below 50 cells / µL. AIDS-defining conditions may be defined as opportunistic illnesses which occur frequently or more severely secondary to immunodeficiency. These include mainly opportunistic infections (Pneumocystis jirovecii), malignancies (Kaposi's sarcoma, lymphoma) & conditions without other evident causes, related to uncontrolled HIV infection. Prior to the introduction of combination ART, AIDS-associated illnesses were the chief aetiology of morbidity and mortality associated with HIV infection.

In the present era of highly active anti-retroviral therapy (HAART), the causes of mortality in addition to opportunistic illnesses like tuberculosis, Pneumocystis jiroveci pneumonia include adverse events to therapy such as anemia, hepatotoxicity and immune reconstitution syndrome. Hence, there is an increased mortality and morbidity burden in patients infected with HIV/AIDS secondary to both disease and therapy; the requirement for monitoring in patients after initiation of ART is as vital as in ART – naïve patients. The median survival of patients with advanced HIV infection (CD4 cell count <50 cells/microL) is 12 to 18 months in the absence of antiretroviral

therapy. Most patients who die of AIDS-related complications have CD4 cell counts in this range.

An effective screening programme aids in rapidly identifying people with HIV/AIDS and hastens the initiation of antiretroviral therapy (ART); additionally, opportunistic infections can be prevented or treated depending on the extent of HIV infection, other comorbidities such as haematological abnormalities like leucopenias or anemia can be detected and managed appropriately.

4.5 CLASSIFICATION OF AIDS

AIDS has been classified into 4 clinical stages in accordance with criteria set down by the World health Organisation (WHO) with increasing severity from stage I to stage IV. The stages are as given under(9) :

- **Primary HIV infection** – This stage consists of asymptomatic infection or an acute retroviral syndrome. An acute retroviral syndrome is usually manifested in the form of an acute febrile illness 2-4 weeks after exposure to the virus. It is usually accompanied by lymphadenopathy, pharyngitis and skin manifestations. Core p24 antigen may be detectable with high blood HIV RNA. Blood abnormalities like a profound temporary lymphopenia may be detected. Seroconversion from HIV antibody negativity to positivity usually occurs during this phase.

- **Clinical Stage I** – It may be either asymptomatic or characterised by persistent generalised lymphadenopathy which refers to lymph nodes which are swollen to a size > 1 cm in two or more non- contiguous sites, excluding inguinal nodes, in the absence of a known cause.

- **Clinical Stage II** – It comprises of patients presenting with moderate (< 10 % of presumed or measured body weight) unexplained weight loss. It is also characterised by other characteristic infections such as :

    a. Recurrent presumed bacterial RTI (two or more in any six-month period)
    b. Herpes zoster
    c. Angular cheilitis
    d. Recurrent oral ulcerations occurring twice or more in six months - aphthous ulceration, with a halo of inflammation and a yellow-grey pseudo-membrane.
    e. Papular pruritic eruptions
    f. Seborrhoeic dermatitis
    g. Fungal paronychia

- **Clinical Stage III** – This phase is characterised by the following clinical features :

a. Severe unexplained weight loss (more than 10% of presumed or measured body weight).
b. Unexplained chronic diarrhoea for longer than one month.
c. Unexplained persistent fever (intermittent or constant and for longer than one month).
d. Oral candidiasis
e. Oral hairy leucoplakia
f. Pulmonary TB (current or in last two years)
g. Severe presumed bacterial infection (e.g. pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia)
h. Acute necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis.
i. Unexplained anaemia (< 8 g/dl), neutropenia (<1000/mm^3) or thrombocytopenia (< 50000/mm^3) for more than one month.

❖ **Clinical Stage IV** – This stage is characterised by the following :

a. HIV wasting syndrome - Unexplained weight loss > 10% of body weight accompanied by visible thinning of face, waist and extremities; in addition, either unexplained chronic diarrhoea (lasting > one month) or unexplained prolonged or intermittent fever (Documented temperature of 37.5 °C or more on occasions with no obvious foci of disease, negative blood culture, negative malaria slide and normal or unchanged CXR) for one month or more.

b. Pneumocystis pneumonia
c. Recurrent severe or radiological bacterial pneumonia (two or more episodes within one year)
d. Chronic herpes simplex virus (HSV) infection (orolabial, genital or anorectal of more than one month, or visceral of any duration)
e. Oesophageal candidiasis
f. Extra-pulmonary / Disseminated TB
g. Kaposi's sarcoma
h. CMV (retinitis or CMV infection of an organ other than liver, spleen or lymph nodes)
i. CNS toxoplasmosis
j. Cryptococcal meningitis or other extrapulmonary Cryptococcus infection
k. HIV encephalopathy
l. Disseminated non-tuberculous mycobacteria infection
m. Progressive multifocal leukoencephalopathy
n. Candidiasis of trachea, bronchi, lungs
o. Cryptosporidiosis (with diarrhoea lasting more than one month)
p. Isosporiasis
q. Any disseminated mycosis (e.g. coccidiomycosis, histoplasmosis, penicilliosis)
r. Recurrent non-typhoidal salmonella septicaemia (two or more episodes in last year)

s. Lymphoma (cerebral or B cell non-Hodgkin)

t. Invasive cervical carcinoma

u. Visceral leishmaniasis

Opportunistic illnesses usually occur when the CD4 cell count falls to levels below 200 cells/ µL but need not necessarily be so. The half-life of the virus in human serum is approximately 1.2 days, about 24 hours in an intracellular milieu, and about 6 hours extracellularly. The daily turnover of the virus is equivalent to about 30 % of the total body viral burden. But in contrast, only 6 - 7 % of the total CD4 cells turns over each day. Hence, AIDS occurs secondary to continuous, high-level replication of HIV, causing virus and immune-mediated destruction of CD4 T cells.

4.6 EPIDEMIOLOGY- GLOBAL

HIV related research has progressed a long way since the first case of HIV was diagnosed in 1981 and the subsequent identification of the virus in 1983. (10) Azidothymidine (AZT) was the first drug discovered to have therapeutic benefit in HIV infection in 1987 followed by the advent of combination retroviral therapy in 1992.(11)(12) The World Health Organisation (WHO) has recorded 31.8 million [30.1 million – 33.7 million] adult patients as infected with the Human Immunodeficiency Virus (HIV) with 1.9 million [1.7 million – 2.1 million] people diagnosed for the first time, as per the global summary of the AIDS epidemic (2013).(1) As is evident from these figures, HIV/AIDS still remains a vital global health issue.

4.7 EPIDEMIOLOGY – INDIAN

The first patient in India was identified in 1986 following a serological analysis among commercial sex workers in Tamil Nadu in southern India.(13) The National AIDS Control Organisation (NACO) statistics reveal that India has the third highest number of people infected with HIV in the world. The prevalence has been projected to be approximately 20.89 lakh, with 0.27 % in the adult age group (15-49 years) in 2011.(2) An overall reduction of 57% in annual new HIV infections among the Indian adult population has been documented over the past decade, reflecting the impact of the National AIDS Control Programme (NACP) through its interventional measures and preventive programmes. (2)

Tamil Nadu is the eleventh largest state in India in terms of area and the seventh most populous state in the country.(14)(15) An estimated 132,590 people (110,563 – 161,038) people with HIV live in Tamil Nadu with approximately 3148 cases diagnosed annually.(16)

Table 1 . Estimates of HIV infection from 2007 -2011 in Tamil Nadu(16)

	2007			2008			2009			2010			2011		
Indicator	**Lower Bound**	**Estimate**	**Upper Bound**	**Lower Bound**	**Estimate**	**Upper Bound**	**Lower Bound**	**Estimate**	**Upper Bound**	**Lower Bound**	**Estimate**	**Upper Bound**	**Lower Bound**	**Estimate**	**Upper Bound**
Estimated No. of PLHIV															
Total	1,37,503	1,61,400	1,85,446	1,29,529	1,52,101	1,76,283	1,21,964	1,44,030	1,70,483	1,15,826	1,37,458	1,64,585	1,10,563	1,32,590	1,61,038
Children (<15 yrs)	5,468	6,940	8,785	5,488	6,959	8,740	5,454	6,922	8,749	5,317	6,761	8,557	5,143	6,504	8,205
Adults (15-49 yrs)	1,22,415	1,43,101	1,66,153	1,14,350	1,34,027	1,57,143	1,06,794	1,25,940	1,49,605	1,00,006	1,19,180	1,42,664	94,315	1,13,911	1,38,535
Elderly (>49 yrs)	9,620	11,359	10,508	9,691	11,115	10,398	9,716	11,168	12,129	10,503	11,517	13,364	11,105	12,175	14,298
Male		1,13,447			1,06,346			1,00,371			95,411			91,705	
Female		47,954			45,666			43,658			42,044			40,885	

4.8 ANTI-RETROVIRAL THERAPY

Highly active antiretroviral therapy (HAART) is essential for management of patients with HIV infection. The EuroSIDA study compared the early ART period to pre-ART and later ART treatment periods, and showed a reduced mortality and progression to AIDS on continuous ART. Widespread use of ART has resulted in a marked decline in the incidence of most AIDS defining conditions and mortality both in the developed and developing world.(3) Suppression of HIV replication is essential to prevent HIV associated morbidity and mortality; it also improves the quality of life in patients with HIV infection. Strict adherence to antiretroviral therapy is required for adequate suppression of HIV infection.(3)

There are more than 25 antiretroviral medications from six major classes currently available for the management of HIV-infected patients. The efficacy of many different combination regimens has been studied to determine the optimal approach to treatment. Multiple comparative clinical trials have found that combination therapy, consisting of two nucleoside reverse transcriptase inhibitor (NRTI) agents plus a third active drug from a different class, is most effective in suppressing HIV RNA, minimizing drug toxicity, and/or reducing HIV-related morbidity and mortality.

The major classes of antiretroviral drugs are as given below:

1. Nucleoside reverse transcriptase inhibitors (NRTIs)
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
3. Protease inhibitors (PIs)
4. Integrase inhibitors (INSTIs)

5. Fusion inhibitors (FIs)
6. Chemokine receptor antagonists (CCR5 antagonists)

The CD4+ cell count thresholds for HAART initiation were recently raised from 350 to 500 cells / mL in the United States and from 200 to 350 cells / mL in mid- and low-income countries. Data suggest that these recommendations mean a substantial increase in the number of patients who will require treatment and need early HIV testing. HAART provides effective treatment options for treatment-naive and treatment-experienced patients. Each class targets a different step in the viral life cycle as the virus infects a CD4+ T-lymphocyte or other target cell. The use of these agents in clinical practice is largely dictated by their ease or complexity of use, side-effect profile, efficacy based on clinical evidence, practice guidelines, and clinician preference.

Resistance, adverse effects, pregnancy, and coinfection with hepatitis B virus, or hepatitis C virus present important challenges to clinicians when selecting and maintaining therapy.

Several toxic syndromes are commonly associated with the use of anti-retrovirals in resource-limited settings. Some of the adverse events associated with the use of these drugs have been listed below in some detail so as to enable us to understand the risks and benefits to be borne in mind prior to initiation of these medications.

Hyperlactatemia and lactic acidosis syndrome — Hyperlactatemia causing symptoms in PLHIV following the use of anti- retroviral medications, and the lactic acidosis syndrome have been linked to chronic use of nucleoside reverse transcriptase inhibitors (NRTIs), which can consequently lead on to mitochondrial toxicity. Clinical manifestations secondary to a significant increase in serum levels of lactates include nausea, vomiting, abdominal bloating, fatigue, weight loss, and hepatomegaly. Hyperlactatemia may cause symptoms in patients and elevated lactate levels, while lactic acidosis causes severe metabolic derangement as a result of unfavourable changes in systemic pH.

Mitochondrial toxicity is a potential risk of long term use of any of the members of the NRTI class. The agents which have been detected to be closely associated with lactic acidosis include stavudine and didanosine. Zidovudine use has also been found to cause lactic acidosis after chronic use . The combination of stavudine and didanosine carries a greater risk than either of these agents being used in isolation. Rare cases of mitochondrial toxicity have been reported with other agents such as abacavir and the nucleotide tenofovir; these agents are not commonly used in resource depleted settings due to economic constraints.

Risk factors for lactic acidosis as noted in the developed world, include female gender, obesity, and stavudine use (17):

- As per a prospective study conducted in Botswana among 650 ART-naive HIV-infected adults initiated on NRTI-containing ART to study patients for

ART-associated toxicities, during the study period and after nearly two years of follow-up, 2 % developed moderate symptomatic to severe symptomatic hyperlactatemia, which was defined in the study as serum lactate >4.4 mmol/L; lactic acidosis (which was defined in the study as symptomatic hyperlactatemia in addition to either a pH <7.35 or serum bicarbonate level <20 mmol/L) developed in 1 % of the study subjects.(17)

- In another study which was conducted as a retrospective analysis of 1735 adults (of which 63 % were female subjects) initiated on ART in Soweto (South Africa), the incidence of lactic acidosis was found to be similar (~ 1.3 %). (18)

The incidence of lactic acidosis in resource-limited settings has been observed to be higher than the 0.1 - 0.4 % as described in studies which were conducted in resource-rich settings, and may be considered a reflection of the frequent use of stavudine in resource depleted regions. Mortality rates from different studies have varied from 7 to 30 percent; patients with a lower body weight (<45 kg) and higher levels of lactate have been noted to have increased rates of mortality in one study.(19)

Serum lactate and pH determination are the diagnostic tests that are performed in patients with suspected lactic acidosis syndrome in resource-rich settings. In areas which have limited laboratory facilities, the anion gap may be simply calculated from

serum sodium, bicarbonate and chloride.(17) In areas where laboratory monitoring are not easily available, clinical suspicion of lactic acidosis (eg, symptoms of nausea, vomiting, abdominal discomfort, weight loss, fatigue) should prompt immediate discontinuation of antiretroviral therapy. An increased anion gap would be evidence in support of lactic acidosis syndrome.

As per a study conducted among 56 patients with mitochondrial toxicity which was associated with stavudine use, switching to zidovudine-containing ART was found to be safe.(18) Since antiretroviral medication selection is mainly limited to older NRTIs in many resource depleted areas, data of this nature may be helpful in drug selection.

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Pancreatitis — Dideoxynucleoside analogues (didanosine and stavudine) are the antiretroviral agents which have been most closely associated with pancreatitis.(20) Differential diagnoses for antiretroviral-induced pancreatitis are pancreatitis secondary to other etiologies such as alcohol use, hyperlipidemia, and cholelithiasis; antiretroviral-induced pancreatitis may be aggravated by other causes such as those mentioned above. Clinical features of pancreatitis include severe abdominal pain radiating to the back, nausea and vomiting. Severe pancreatitis can be fatal, especially if associated with a lactic acidosis syndrome.(17)

In resource-deficient settings, the net rate of confirmed pancreatitis is comparatively low in studies, although the limited availability of diagnostic tests may affect the

ability to diagnose this complication. 1029 patients with advanced AIDS in a home-based care program in rural Uganda were followed for clinical signs of antiretroviral toxicity without any facility for laboratory monitoring.(21) Despite almost all patients being initiated on stavudine-containing ART, only 0.3 percent received a clinical diagnosis of pancreatitis following a total of 11,268 patient-months of observation. In stark contrast, a retrospective study that was conducted in a resource-rich setting detected that the incidence rate for clinical and/or chemical pancreatitis in patients who were receiving stavudine-containing regimens ranged from 0.77 - 1.84 per 100 person-years, which was considerably higher than in the Uganda study.(20)

The combination of low body weight and the didanosine use may cause a resultant increase in the risk of pancreatitis. In a retrospective review of 575 patients who had been treated with tenofovir and didanosine (this is a combination that is no longer recommended), didanosine alone, or tenofovir alone, all 6 cases of pancreatitis were reported in patients who were female, weighed < 60 kg and received didanosine, either alone (n = 1) or in addition to tenofovir (n = 5).(22)

Peripheral neuropathy — Stavudine and didanosine are antiretroviral agents that are most frequently associated with peripheral neuropathy closely followed by nevirapine.(23) Other causes of peripheral neuropathy include advanced HIV infection itself, aging, diabetes, and nutritional deficiencies. Concomitant use

of isoniazid or other neurotoxic medications may further increase the risk of peripheral neuropathy.

Unlike the relatively low percentage of patients who develop lactic acidosis or pancreatitis while receiving these agents, peripheral neuropathy occurs in a high percentage of patients, both in resource-rich and resource-poor countries(24):

- In a Kenyan cohort of 1286 patients followed for nearly two years on ART (generally stavudine, lamivudine, and nevirapine), 54 percent switched ART regimens; 21 percent of these patients switched because of symptoms of peripheral neuropathy.(25)
- In a small study of 102 treatment-naive HIV-infected Ugandan patients and 25 HIV-seronegative controls, 54 percent of the treated patients reported foot numbness after six months of stavudine-containing ART, including 38 percent of those with no symptoms at baseline.(26)
- In a cohort of 199 HIV-infected Kenyans, women were almost 10 times more likely to develop peripheral neuropathy than men during one year of follow-up, after controlling for other factors, such as CD4 cell count, body mass index, ART regimen, and tuberculosis treatment.(27)

Despite concerns about stavudine-induced neuropathy, the mortality benefits of ART outweigh potential neurologic morbidity when no medication alternatives exist. As noted above, in an effort to reduce adverse effects, the WHO has reduced the

recommended starting dose of stavudine in adults to 30 mg twice a day regardless of body weight.(28)

In patients who develop this complication, replacement of stavudine with less toxic agents, such as tenofovir, is suggested when feasible, since switch strategies to alternative agents have been associated with improvements in mitochondrial DNA content and mitochondrial morphology in resource-rich settings.(29)

Central nervous system effects — Efavirenz may commonly cause acute subjective neurologic symptoms, typically of limited duration, which can impact adherence.

The overall frequency of this complication appears to differ by racial group and may be related to genetic influences on drug metabolism. The cytochrome (CYP)2B6 516G>T polymorphism (referred to as the "T/T genotype")
impairs efavirenz metabolism and occurs more commonly in Africans than in Caucasians. For example, in one study, the T/T genotype was reported in 3 percent of European-Americans compared with 20 percent of African-Americans.(30) In another study of 142 HIV-infected patients from South Africa, the prevalence of this genotype was 13 percent.(31)

The higher prevalence of the T/T genotype among Africans may explain, in part, reports of increased CNS toxicities such as depression, anxiety, and severe sleep disturbance in Africans, since increased symptoms have been directly related to higher serum drug concentrations. If CNS symptoms continue after the first month of

treatment, consideration should be given to an alternative therapy, such as a nevirapine.

Central nervous system effects may also be exacerbated if the standard dose of efavirenz (600 mg) is increased to 800 mg daily, as is sometimes done to counter pharmacologic interactions between efavirenz and rifampin in TB-coinfected patients. However, this dosing strategy has been linked to increased toxicity in patient subsets with the T/T genotype. If a patient develops significant CNS side effects on efavirenz at the 800 mg dose, consideration should be given to dose reduction, particularly if viral suppression has already been attained.

Anemia — Since zidovudine frequently causes anemia, monitoring of hemoglobin is advisable. Anemia generally occurs during the first six months of zidovudine therapy and may be completely asymptomatic (with only macrocytosis as a marker of zidovudine use) or symptomatic with fatigue or dyspnea. In severe cases, zidovudine-induced anemia can present with life-threatening aplastic crisis.

In a study of 3312 treatment-naive patients in Uganda and Zimbabwe, 219 (6.6 percent) on zidovudine-containing regimens exhibited severe anemia (hemoglobin <6.5g/dL) by week 48. This rate is higher than that seen in industrialized nations, and may reflect lower baseline hemoglobin levels secondary to other concomitant infections (such as hookworm or tuberculosis). Women and those with lower baseline

hemoglobin, CD4 cell counts, and body mass index at baseline were at significantly higher risk of developing severe anemia. Reassuringly, the use of cotrimoxazole was not a risk factor for this adverse event.

Where laboratory capabilities allow, assessment for other causes of anemia may also be warranted, such as iron deficiency, medication-induced hemolysis (eg, dapsone), or gastrointestinal bleeding. Parvovirus B19 infection, another potential cause of anemia in HIV-infected patients, has been rarely implicated in resource-limited settings, but this may be related to diagnostic limitations. A study in Brazil found parvovirus B19 IgG seropositivity in 62.8 percent of 261 consecutive HIV-infected patients, and suggested that seronegative patients may be at risk of infection during epidemic periods. If bone marrow infiltration (eg, by lymphoma or Mycobacterium avium complex), or suppression is suspected (eg, medications), a bone marrow biopsy may be indicated, where feasible.

Zidovudine use may be even more problematic in areas with high prevalence of certain parasitic coinfections that can exacerbate anemia, such as malaria or hookworm. Tuberculosis may overshadow parasites as a major contributor to anemia in populations with a high prevalence of HIV/TB coinfection. In this situation, treatment of tuberculosis may lead to overall improvement of anemia. Since a patient with baseline anemia is at higher risk for increasing severity of anemia after initiation

of zidovudine, baseline testing with a spun hematocrit would be helpful if laboratory testing is limited.

Lipodystrophy — With the introduction of effective antiretroviral therapy, descriptions of patients with body shape abnormalities, such as central fat accumulation and peripheral fat loss emerged. The term "HIV-associated lipodystrophy syndrome" was coined, but it soon became clear that some patients have pure lipoatrophy, others have fat accumulation, and a subset of patients have a mixed picture of both morphologic features. Lipodystrophy can also be associated with disorders in glucose and lipid metabolism.

In settings where discrimination is still entrenched, stigmatizing physical features (such as malar atrophy) may be particularly detrimental to adherence and patients' well-being. Risk factors for lipoatrophy include use of stavudine or didanosine, and to a lesser extent, zidovudine.

The frequency of lipodystrophy in resource-limited settings is substantial, which likely reflects the widespread use of medications, such as stavudine, which are prone to cause metabolic and body shape changes, such as lipoatrophy. Two studies from Africa demonstrated prevalence rates ranging from 30 to 70 percent; stavudine was a significant predictor of risk.

Data from developed countries suggest that use of protease inhibitors (PIs) may be a significant factor in lipodeposition; however, there is limited information on the role of PIs in lipodystrophy syndromes in resource-limited settings at this time because this class of antiretrovirals is infrequently prescribed.

Treatment for lipoatrophy is essentially limited to discontinuation of the offending agent; however, clinical improvement is exceedingly slow and full recovery may not necessarily occur.

Hepatotoxicity — All antiretroviral agents can cause hepatotoxicity, although different drugs vary in their propensity to cause liver damage. Of the NRTIs, stavudine and didanosine are the most likely to cause hepatotoxicity, probably because of the mitochondrial effects of these agents. Full-dose ritonavir is the most hepatotoxic of the PIs, but this drug is rarely used at such doses anymore; when used as a low-dose pharmacologic booster of other agents, ritonavir is less commonly associated with liver injury. Of the non-nucleoside reverse transcriptase inhibitors (NNRTIs), nevirapine is more likely to cause hepatotoxicity than efavirenz in patients with detectable viremia. However, in resource-rich settings, nevirapine appears to be relatively safe in patients with viral suppression who are switched to this agent.

The risk of nevirapine hepatotoxicity is concentrated in certain risk groups. In a prospective cohort study of 146 pregnant females in Mozambique, severe

hepatotoxicity was more common in those with CD4 cell count >250 cells/mm3 compared with patients whose CD4 cell count was <250 cells/mm3 (6 percent versus 0 percent). Having a CD4 count >400 cells/mm3 has been identified as a risk factor for nevirapine hepatotoxicity in men; at this time, this finding is less relevant in resource-limited settings because such patients rarely meet current WHO or national guidelines for ART initiation.

Coinfection with viral hepatitis also increases the likelihood of ART-induced hepatotoxicity. For example, in a Nigerian study of 1564 patients, the risk for serious hepatotoxicity 24 weeks after initiation of ART was 3.1 percent in patients coinfected with HBV compared with only 0.5 percent in patients with HIV alone; hepatotoxicity was not associated with either baseline HBV DNA concentration or HBeAg status. Coinfection with hepatitis C is an important risk factor as well, but this diagnosis tends to be more common in resource-rich areas.

Other risk factors for ART-related liver injury include concomitant use of other hepatotoxic drugs (such as antituberculous agents or herbal remedies) and the presence of abnormalities of aminotransferases at baseline.

Hypersensitivity reactions — Though virtually any drug can cause a hypersensitivity syndrome, nevirapine and abacavir are associated with uncommon but well-documented life-threatening reactions. Prior to starting patients on these medications,

the clinician should discuss potential symptoms that would alert the patient to the possibility of this reaction.

Common concomitant medications such as antituberculous medications, trimethoprim-sulfamethoxazole (TMP-SMX), beta-lactam antibiotics, and herbal remedies may provoke hypersensitivity reactions (HSR) as well. Thus, it is important to consider all medications as potential causes.

Nevirapine — This agent accounts for over three-fourths of NNRTI prescriptions in resource-limited settings.(32) Hypersensitivity reactions (HSR) may present with rash, fever, hepatitis, or eosinophilia, usually during the first 16 weeks of therapy. In a Ugandan cohort of 1029 patients studied during a 19-month period, the incidence of nevirapine HSR was 1.7 percent, including one death.(21) Rechallenge with nevirapine is contraindicated after an HSR.

Nevirapine HSR is more common in women with CD4 cell count <250 cells/mm3 and men with CD4 cell count <400 cells/mm3. The risk of nevirapine HSR is related to the pretreatment CD4 cell count and the presence of HIV viremia. Thus, if the patient's CD4 count rises to >250 cells / mm^3 on treatment, nevirapine does not need to be discontinued. Also, the risk of hypersensitivity reaction is mitigated when viral suppression has already been achieved. Thus, switching a patient to nevirapine due to an adverse event related to another drug is much less likely to lead to HSR if viral

suppression has already been achieved.(33) Lead-in dosing (eg, 200 mg daily for 14 days followed by twice-daily dosing) is recommended to decrease the risk of adverse events.

Abacavir — The presence of the HLA-B*5701 allele greatly increases the risk of abacavir HSR, and its absence markedly reduces the risk of an immunologic reaction.

Testing for HLA-B*5701 has become the standard of care in many developed countries, but is rarely available in resource-limited settings. Fortunately, this haplotype is rare in Africans; thus, it appears abacavir can be used relatively safely in this population with close monitoring. Of 599 Ugandan patients, only 2 percent of those randomly assigned to abacavir experienced an HSR compared with 4.7 percent who were treated with nevirapine.(34)

Nephrotoxicity — There is concern that the prevalence of nephrotoxicity may increase as the nucleotide reverse transcriptase inhibitor, tenofovir, becomes more widely available in Sub-Saharan Africa. Tenofovir use has been associated with renal insufficiency, particularly in patients with preexisting diabetes or hypertension.

However, in an observational study of 3316 treatment-naive patients in Zimbabwe and Uganda, despite high prevalence of baseline mild to moderate renal insufficiency and common use of tenofovir (74 percent), severe renal dysfunction after 96 weeks was

rare, and tenofovir-free regimens offered only marginal benefit in improving baseline glomerular filtration rate.(35) This finding is particularly reassuring since prior to treatment, 45 and 7 percent of the patient population had mild or moderate renal insufficiency, respectively.

Tenofovir also has dual activity against hepatitis B and is often prescribed to patients with HBV coinfection in several countries, including South Africa and Nigeria.

Myopathy — In rare cases, diffuse muscle fatigue or weakness, generally of insidious onset, can result from treatment with zidovudine. Patients must be monitored for zidovudine-related myopathy through careful history and physical examination. If laboratory monitoring is available, a creatine kinase should also be checked in suspected cases; when elevated, a muscle biopsy may be considered. Zidovudine should be discontinued if this diagnosis is suspected.

Rash — Skin eruptions are a common complication of NNRTIs, such as efavirenz and nevirapine. A case-control study was performed among Thai patients who developed rash after starting nevirapine-containing ART compared with patients who did not.(36) Risk factors for the development of rash included a prior history of drug allergy and low body weight; risk was also elevated with higher CD4 cell counts (odds ratio, 1.2 per each 50 cells/mm3 increment).

If a rash occurs, it is generally safe to continue therapy with nevirapine or efavirenz with close monitoring of the patient. However, it is

crucial to distinguish self-limited mild drug rash from life-threatening, systemic reactions, such as Stevens-Johnson Syndrome (SJS) or hypersensitivity reaction (HSR), which have both been described in association with nevirapine and abacavir.(37) Rash that is associated with mucosal involvement (eyes, mouth) suggests SJS, while constitutional symptoms, fever, and eosinophilia suggest HSR.

Consideration should also be given to other potential etiologies of rash, such as medications, concomitant infections (eg, secondary syphilis) or worsening of eczematous rashes or eosinophilic folliculitis during ART-associated immune reconstitution.

Gastrointestinal complications — Protease inhibitors often cause diarrhoea, which may or may not be self-limited. If the diarrhoea persists, opportunistic infections (eg, Mycobacterium avium intracellulare) should be excluded, especially in patients with advanced immunosuppression.

Dyslipidemia and metabolic complications — Abnormal fasting lipid profiles and impaired glucose tolerance are common among patients on ART.(38) In the NRTI class, stavudine and zidovudine are more likely to be associated with dyslipidemia than abacavir or tenofovir. Amongst the NNRTIs, efavirenz is more likely to cause dyslipidemia than nevirapine, which is associated with favorable increases in HDL-c.

Lipid profiles were monitored at 12 and 24 months after the initiation of ART in 374 patients in Uganda, the vast majority of whom were taking stavudine, lamivudine, and nevirapine.(39) After 24 months, increases in HDL-cholesterol levels were substantial and proportionally greater than increases in total cholesterol or LDL-c levels, which were likely related to nevirapine.

Cardiovascular events — Cardiovascular disease is prevalent in many resource-limited settings and traditional cardiac risk factors may be on the rise. According to statistics from the WHO, cardiovascular deaths (including coronary artery disease and cerebrovascular disease) comprise 15 percent of all deaths in low-income countries, substantially greater than the 5.7 percent of deaths from HIV/AIDS.(40) A survey performed among persons living in rural and urban communities in South Africa assessed the influence of urbanization on nutritional status and overall health.(41) This study documented that those living in urban settings had elevated levels of LDL-c and total cholesterol, higher rates of obesity, and significantly higher proportions of persons with elevated systolic blood pressure than those living in rural areas.

Abacavir and didanosine have been associated with an increased likelihood of myocardial infarction in some studies in resource-rich settings, though these associations remain controversial and the underlying mechanisms have not been conclusively elucidated.(42) Further research is needed to define the impact of antiretroviral medications on cardiovascular disease in low-income nations undergoing lifestyle changes as a result of industrialization.

Special considerations during pregnancy — Females of childbearing potential are disproportionately affected by HIV infection in resource-limited settings. Pregnancy is common because many infected men and women remain sexually active in the absence of effective contraception and there are strong social pressures to procreate.(43) The teratogenic potential of certain antiretroviral medications and the use of nevirapine in pregnancy for maternal health or prevention of mother-to-child transmission are reviewed elsewhere. Due to neural tube defects observed in monkey studies and a few clinical cases observed in humans, efavirenz is classified as a Pregnancy Category D drug and is best avoided in women who are planning to or may become pregnant.

4.9 IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

"Immune reconstitution inflammatory syndrome" (IRIS) describes a collection of inflammatory disorders associated with paradoxical worsening of pre-existing infectious processes following the initiation of highly active antiretroviral therapy (HAART) in HIV-infected individuals.(44) Pre-existing infections in individuals with IRIS may have been previously diagnosed and treated or they may be subclinical and later unmasked by the host's regained capacity to mount an inflammatory response.(45)

If immune function improves rapidly following the commencement of HAART, systemic or local inflammatory reactions may occur at the site or sites of the preexisting infection. This inflammatory reaction is usually self-limited, especially if

the preexisting infection is effectively treated. However, long-term sequelae and fatal outcomes may rarely occur, particularly when neurologic structures are involved.

It is generally accepted that the diagnosis of IRIS requires the worsening of a recognized ("paradoxical" IRIS) or unrecognized pre-existing infection ("unmasking" IRIS) in the setting of improving immunologic function. Most or all of the following features should be present in order to make the diagnosis:

- The presence of AIDS with a low pretreatment CD4 count (often less than 100 cells/microL). One important exception to this general rule is tuberculosis. IRIS secondary to pre-existing M. tuberculosis infection may occur in individuals with CD4 counts >200.
- A positive virologic and immunological response to ART.
- The absence of evidence of drug-resistant infection, bacterial superinfection, drug allergy or other adverse drug reactions, patient noncompliance, or reduced drug levels due to drug-drug interactions or malabsorption after appropriate evaluation for the clinical presentation.
- The presence of clinical manifestations consistent with an inflammatory condition
- A temporal association between HAART initiation and the onset of clinical features of illness

One prospective study found that patients developed IRIS within a median of 48 days (29 to 99 days).(46)

When a diagnosis of IRIS is considered highly likely, further or repeated invasive diagnostic procedures to locate an occult infection may be reasonably delayed, deferred, or altogether avoided. However, localized drainage (with appropriate cultures) is indicated for symptomatic relief of mycobacterial lymphadenitis as well as for diagnostic purposes.

4.10 NATIONAL AIDS CONTROL PROGRAMME

ART has been dispensed free of cost under the National AIDS Control Programme (NACP II) since April 2004. More than 300 ART centres are functional in India at present and more than 516,000 patients are receiving ART at these centres. Approximately 30,000 patients receive free ART in the private sector.(4) Consequently, there has been a progressive decline in annual AIDS related mortality with an estimated 1.5 lakh lives being saved due to ART till 2011.(2) The number of ART centres is gradually being scaled up in a phased manner.

4.11 MORTALITY IN HIV / AIDS

In most patients infected with HIV on adequate treatment with antiretroviral therapy (ART),

the incidence of AIDS-defining events is very low, with often undetectable HIV-RNA levels on available assays. Despite adequate treatment with ART, excess mortality has been observed in these individuals as compared to matched controls and

is not explained by parameters like CD4 count alone. Studies like the SMART trial point towards probable etiologies such as HIV-associated inflammation with increased risk of hypercoagulability and aging-associated organ system injury.(5) In this trial, HIV-infected persons were randomized to continuous ART or therapy guided by CD4 T cell counts. Subjects randomized to interrupted therapy had a higher risk of morbidity and mortality than subjects on continuous therapy. Interruption of ART regimens resulted in a rapid rise in inflammation and coagulation related biomarkers which correlated with an increased risk of death, AIDS, and cardiovascular disease (CVD). The mechanisms which link HIV replication to inflammation, coagulopathy, and disease progression remain largely undefined.(47) There has been an increasing body of evidence suggesting that the risk of serious non-AIDS conditions like cardiovascular disease (CVD), renal or hepatic disease and non-AIDS defining malignancies is increased in people with HIV infection as compared to matched controls.(6) Multiple trials have been conducted to assess correlation of non-traditional with traditional markers of inflammation to monitor patients with potentially modifiable risk factors.

4.12 NEED FOR PROGNOSTIC INDEX

Physicians treating patients with HIV infection are frequently asked for prognostic assessments and quality of life after initiating therapy. Prognostic systems such as risk factors, staging systems, statistical models, and computer algorithms have been developed to standardize and enhance the accuracy of prognostic assessments.

Although diverse techniques are used to develop these systems, all use a sample of patients for whom the outcome is known to relate baseline characteristics to an outcome of interest. Once a system is developed, it can be used to generate predictions for patients whose outcome is not yet known. A common problem in the application of prognostic systems is that the accuracy of the predictions degrades from the sample in which the system was first developed to subsequent application; that is, the systems do not generalize .(48)

4.13 THE VETERANS AGING COHORT STUDY (VACS) INDEX

The Veterans Aging Cohort Study (VACS) is a longitudinal, prospective multi-site observational study of HIV infected and uninfected patients evaluated in Veterans Administration Medical Centre (VAMC) infectious disease and general medical clinics.(49) The Veterans Aging Cohort Study (VACS) Risk Index was designed to predict mortality in HIV patients who have been treated for one year, using a simple scoring system. It was intended to take into account all possible interactions of HIV disease, comorbidities, substance abuse, and adverse drug reactions secondary to treatment, on outcome in HIV-infected patients.(7) As most patients would be on ART for extended periods, an on-treatment index was considered to be more relevant to health professionals and HIV positive people, for evaluating prognosis after initiation of therapy. There was also a possibility of an alteration in reported relationships between known biomarkers and mortality subsequent to initiation of treatment. (5)

It was developed in HIV-infected US veterans and validated in independent cohorts from the US and Europe participating in the Antiretroviral Therapy Cohort Collaboration (ART-CC).(5) Prognostic indices were developed using data from a cohort of more than 33,000 HIV-infected veterans for whom data on inpatient and outpatient diagnoses, laboratory results, and pharmacy dispensations were documented during routine clinical visits starting from the initial visit. VACS included all HIV-infected Veterans in Veterans Administration (VA) care. Development and validation datasets were combined to evaluate index performance within important patient subgroups [women, those with HIV-1 RNA<500 copies/ml, and Hepatitis C (HCV) co-infected patients]. (5)

The VACS index comprised of the following prognostic factors – age of the individual in years, CD4 count, HIV-1 RNA, haemoglobin, aspartate transaminase (AST) & alanine transaminase (ALT) levels, platelets, creatinine and HCV status.

Two composite markers of hepatic injury (FIB-4) and renal injury (eGFR) were derived from the constituent parameters of the VACS index. FIB-4 has been validated as an indicator of liver fibrosis and is calculated using age, AST, ALT & platelets. Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or

>3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86 %.

FIB-4 ={age(in years) x AST}/(platelets in 100/L x √ ALT)

The estimated glomerular filtration rate (eGFR) is calculated using the Modification of Diet in Renal Disease (MDRD) equation as given under:

eGFR =186.3 x $(\text{creatinine})^{-1.154}$ x $(\text{age})^{-0.203}$ x (0.742 for women) x (1.21 if Black).

This equation has been validated as a marker of impaired renal function.

The HCV infection status was derived from a documented diagnosis based on a positive antibody test or detectable plasma HCV-RNA in the patient's medical records. The patients were assumed to remain either positive or negative after being tested once.

During the initial days of the study, in the time period between 1st January 1997 and 1st August 2002, the original VACS index consisted of, in addition to the components already mentioned above, AIDS-defining conditions, hepatitis B serology and substance abuse or dependence (alcohol or drugs).(50) As AIDS events were uncommon among those on ART and had a variable association with mortality and

also, the diagnoses of substance abuse and hepatitis B infection were inconsistently measured across cohorts, the index was narrowed down to the present components.(51)(52)

The VACS index was compared with a Restricted Index that included only age and conventional HIV risk factors (CD4 count and HIV-1 RNA) in the same cohort. Each prognostic factor was categorized into levels for convenience in future application in clinical settings. The number of categories of CD4 count, HIV-1 RNA, anaemia and renal function were expanded compared with previous analyses. The score can be used to estimate risk of all-cause mortality using a conversion factor. The individual clinical parameters were considered as categorical measures; the score was weighted to indicate an increasing risk of all-cause mortality with increasing score.

Table 2.Components of the VACS Index

		Points
Age (years)	< 50 50-64 ≥65	0 12 27
CD4-cell count, cells/mm^3	≥500 350-499 200-349 100-199 50-99 <50	0 6 6 10 28 29
HIV-1 RNA, copies/ml	<500 500-1X10^5 ≥ 1X10^5	0 7 14
Haemoglobin, g/dl	≥14.0 12.0-13.9 10.0-11.9 <10	0 10 22 38
FIB-4	<1.45 1.45-3.25 >3.25	0 6 25
eGFR, ml/min	≥60 45.0-59.9 30.0-44.9 <30	0 6 8 26
Hepatitis C infection		5

FIB 4 : (years of age x AST)/(platelets in 10^9/L x √ ALT). eGFR : 186.3 x (creatinine)$^{-0.154}$ x (age)$^{-0.203}$ x (0.742 for women) x (1.21 if Black) ALT. alanine transaminase; AST, aspartate transaminase; cART, combination antiretroviral therapy; eGFR, estimated Glomerular Filtration Rate; FIB - Fibrosis Index; IQR-inter-quartile range. Hepatitis C diagnosis, positive antibody test or detectable virus. (53)(5)

The Christian Medical College (CMC) Vellore has been involved in HIV care and training right from the onset of the HIV epidemic in India in 1986. Medicine Unit I and Infectious Diseases currently take care of over 44,118 outpatients and 2217 inpatients annually. Interdisciplinary Infectious Disease (ID) Clinic involving Medicine, Paediatrics, Dermatology and STD and Social Work provides comprehensive care to about 3873 HIV patients every year. The department also conducts support group meetings for HIV positive people to provide social support to the patient and their families as well as provides income generation assistance. The Obstetrics and Gynaecology department of the hospital runs Prevention of Parent to Child Transmission (PPTCT) which provides counselling for couples who visit the antenatal clinic. Interventions to reduce vertical transmission of HIV are provided to HIV positive mothers. Free ART drugs are provided to HIV infected people through ACTFID (ACC-CMC Trust for Infectious Diseases) and with assistance of NACO.(54)

In view of the probability of increased mortality despite being compliant with the best available ART, the need for a reliable prognostic indicator was felt. The target population treated by the ID clinic and receiving ART from the NACO - ART centre was different in terms of their epidemiological characteristics from the constituent population of the VACS cohort. Patients from both the paediatric and adult age group come under the purview of the ART centre.

The VACS Index integrates nine component parameters into a single score which aids in reflecting the disease burden of the patient. A composite index such as the VACS index has a few major advantages as compared to individual biomarkers. First, a score gives the clinician an overall sense of the patient's condition and can be used to predict the progress of the patient's clinical condition including increased or decreased risk of morbidity or mortality. While prognosis could also be obtained by entering individual values into a risk calculator, the simplicity of a single number is appealing for ease of interpretation by both clinician and patient. Second, thresholds for concern of these routinely monitored measurements have typically been more extreme than those identified by the index. The exercise of calculating the integrated impact of several biomarkers can help clinicians recognize the importance of more moderate abnormalities that may still be associated with disease.(5)

5. METHODS

5.1 SETTING

The Christian Medical College, Vellore, is a 2000 bedded, tertiary care centre in South India. The Department of Medicine Unit-I and Infectious disease has been providing care to PLHIV from the beginning of the HIV epidemic in India in 1986. An interdisciplinary infectious disease clinic runs on Wednesday afternoon and two full OPD days on Tuesday and Friday, involving medicine, pediatrics, dermatology and venereology and social work which provides comprehensive care to PLHIV.

Patients were recruited from referrals to the NACO – ART centre from the Infectious Diseases (ID) clinic. The ART centre in the Christian Medical College Vellore was inaugurated in 2008 and has an annual turnover of approximately 4000 HIV patients every year. The ID clinic evaluates patients of all age groups diagnosed with HIV infection/AIDS, predominantly from the South Indian states of Tamil Nadu, Andhra Pradesh and Karnataka, with an interdisciplinary team from Medicine, Paediatrics and Dermatology.

5.2 STUDY DESIGN

Our study recruited subjects **by retrospective analysis** from old electronic medical records into **a cohort** from the **time period 1st June 2012 to 31st May 2013.**

The duration of follow up of the patients was two years beginning **from 1st June 2013 and ending on 31st May 2015.**

The sample size was calculated using the assumptions made below:

- $n = \frac{Z * p * q}{d^2}$

Z = Standardized normal deviate

p = proportion / prevalence of mortality in population of interest

q = 100 – p

d = Clinically expected variation

For the year 2012 –2013, the total population of PLHIV started on first line NACO – ART was 353 with an outcome of mortality in 31.

Prevalence of mortality (p) = 31/353 = 8.8 %

Anticipating a clinical variation (d) of 3.5%, and a Z – value for a 95 % confidence interval corresponding to 1.96,

- $n = \frac{(1.96)^2 \times 8.8 \times 91.2}{(3.5)^2} = 252$

5.3 INCLUSION CRITERIA

- PLHIV started on first line NACO ART regimen from ID clinic in CMC Vellore during the period from 1st June 2012 to 31st May 2013.

5.4 EXCLUSION CRITERIA

- PLHIV started on ART before or after the specified period (1st June 2012 – 31st May 2013).
- PLHIV started on non-NACO ART.

5.5 VARIABLES

After recruitment, baseline blood investigations with other patient related information such as age and gender were used to complete the clinical research form. The data filled in the proforma included the following variables:

- Age
  - < 50 years
  - 50 - 64 years
  - ≥ 65 years

- Gender
  - Male

- Female

- CD – 4 count

  - >500 /mm^3
  - 350 – 499 /mm^3
  - 200 – 349 /mm^3
  - 100 – 199 /mm^3
  - 50 – 99 /mm^3
  - < 50 /mm^3

- Haemoglobin

  - > 14 g / dl
  - 12 – 13.9 g / dl
  - 10 – 11.9 g / dl
  - < 10 g / dl

- AST
- ALT
- Platelets
- Creatinine → eGFR
- Hepatitis C infection

The AST, ALT and Platelets count were used to derive a composite variable called the FIB-4. The formula for calculation of the FIB-4 index is as given below:

FIB-4 = {Age (in years) x AST}/(Platelets in 100/L x √ ALT)

Details with regard to the validity of the FIB-4 index have already been elucidated in detail in the literature review.

The creatinine, age and gender were used to derive the estimated glomerular filtration rate by using the Modification of Diet in Renal Disease (MDRD) formula as given below:

eGFR =186.3 x $(\text{creatinine})^{-1.154}$ x $(\text{age})^{-0.203}$ x (0.742 for women) x (1.21 if Black).

The HIV – RNA titres were not considered in the Modified VACS Index as it was not feasible to be done on a routine basis for most patients due to the lower socio economic status of the average patient attending the ID clinic and associated financial constraints.

Patients were recruited based on time of initiation of ART which was determined from records of patients initiated on ART maintained at the NACO-ART centre. A list of patients was made and they were actively recruited at the due time of presentation to the ART centre which was also determined based on the documentation in the chart at the previous visit. Outcomes were followed up in a systematic manner at follow up visits to the ID clinic or ART centre.

The study was approved by the institutional review board (IRB) of our hospital in the month of November 2013. Following approval of the study protocol, the study was commenced from January 2014.

5.6 STATISTICAL ANALYSIS

The data was analysed **for association between outcomes (alive or dead) and the modified VACS index (MVI)** and the **components of the MVI** viz. age, sex, CD4 cell count, haemoglobin, AST, ALT, platelet count and serum creatinine using **a logistic regression analysis**; if any association was detected, the statistical significance would be ascertained from the p-value (< 0.05) and the 95 % confidence interval. The **predicted mortality** would be calculated with the aid of this logistic regression analysis and **compared with the actual mortality** in the study cohort after a 2 year period utilising a standardised mortality ratio.

Bi-variate analysis was performed between all the individual parameters (and the composite indices – eGFR and the FIB-4) and the outcome at the end of the study period. Outcomes considered were alive at the end of 2 years as compared to death or lost to follow up which

grouped together as a bad outcome. The variables which showed the greater association were utilised for the logistic regression analysis for calculation of a predicted probability of bad outcomes.

All calculations and analysis were done using SPSS version 16.0. Initial tabulation of data was done using an excel spread sheet. Extensive statistical assistance was required during this project for which the author is indebted to the team of statisticians who assisted in this project.

A flow diagram representing the study design and the timeline of the study has been presented as in Figure1:

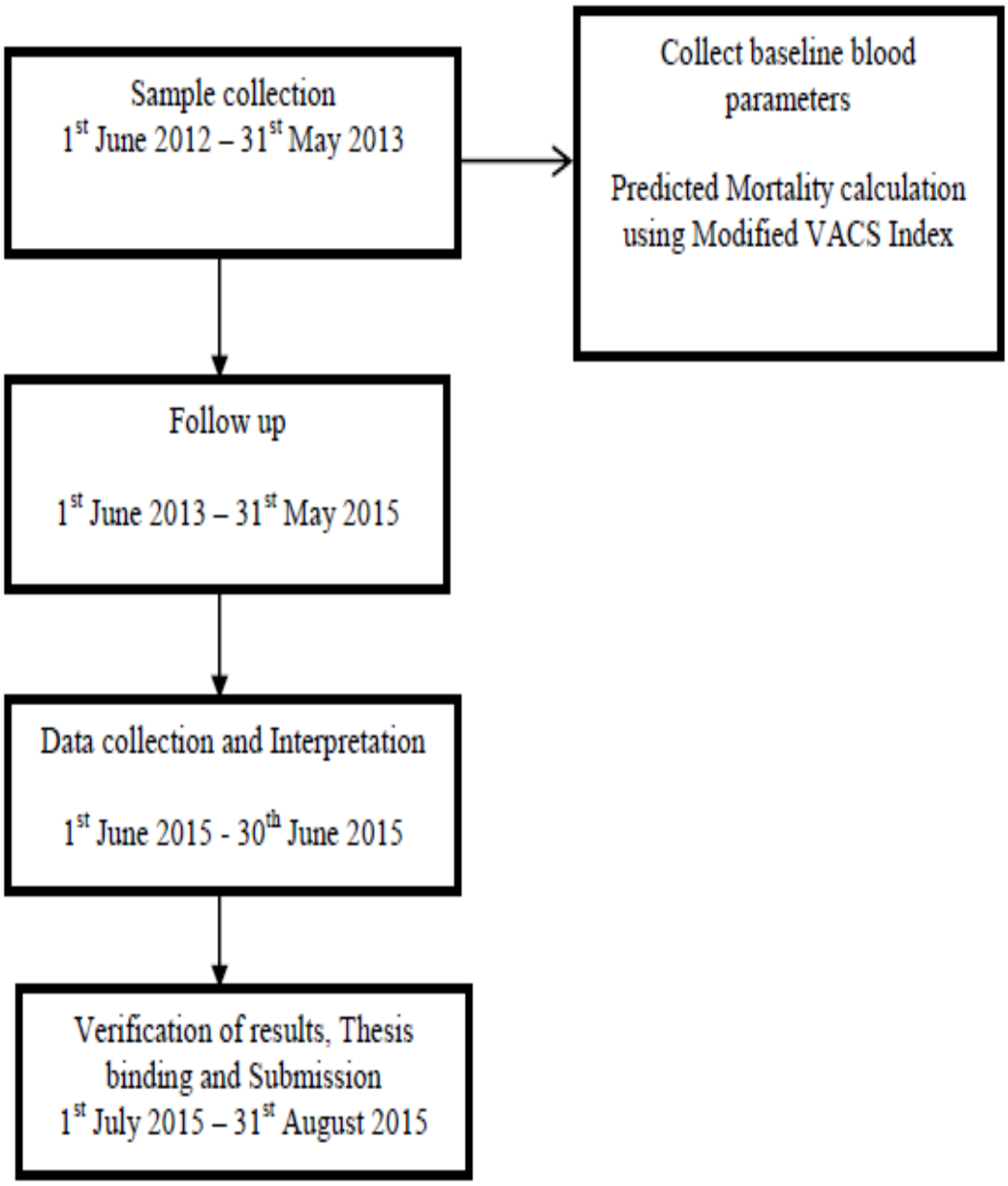
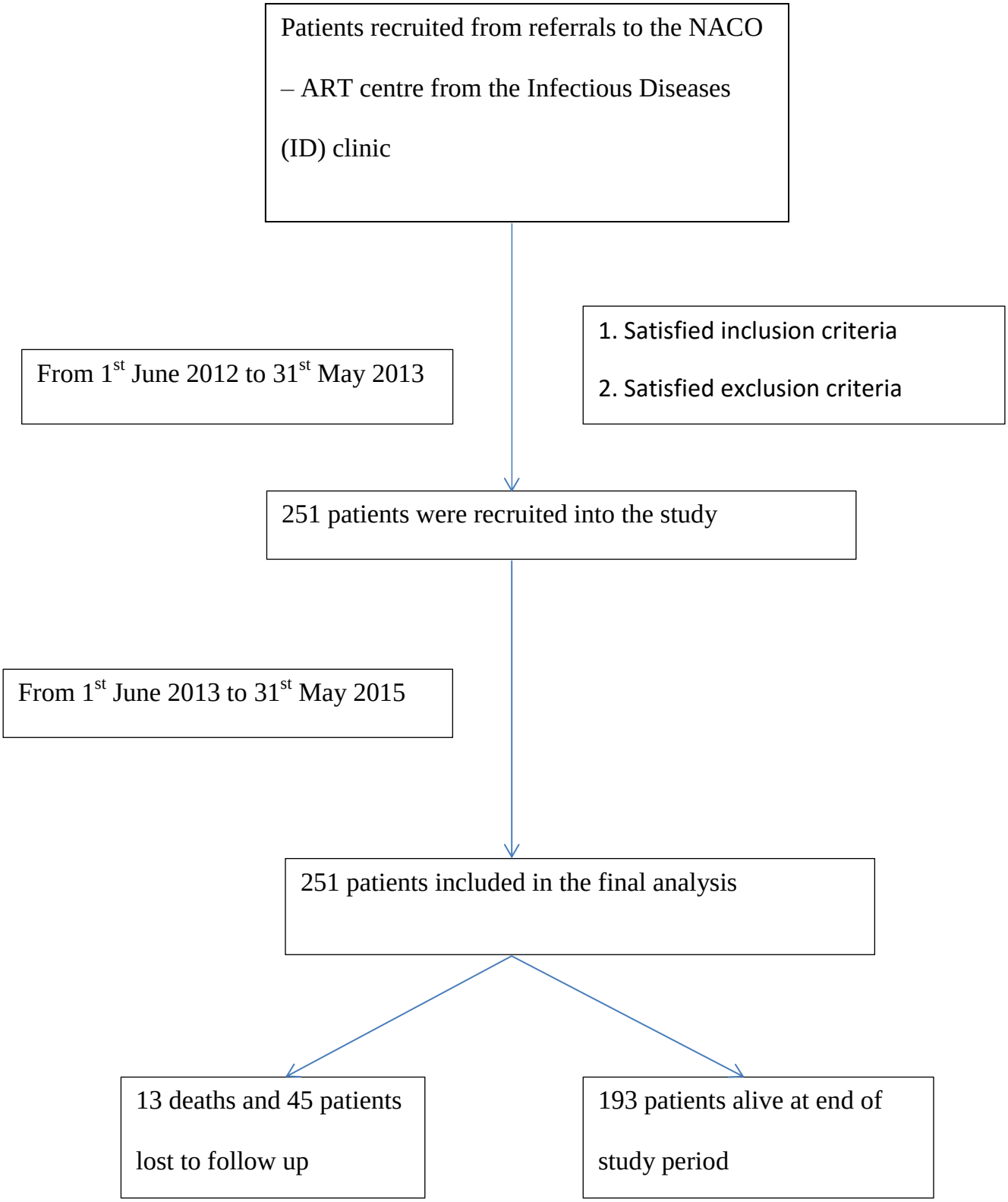


Figure 1a. Timeline of the Study

Figure 1b: STROBE FIGURE



5.7 DIAGNOSTIC ASSAYS

HIV testing was carried out as per WHO / NACO strategy III. The 1st and 2nd assays were 4th generation assays which detect p24 antigen and antibody. The 3rd assay was a 2nd generation assay which was used to differentiate between HIV-1 and HIV-2. In case of discrepancy between the 3 assays, additional assays including plasma HIV-1 RNA estimation was carried out.

CD-4 testing was carried out in a BD FACS count machine as per the manufacturer's instruction. Briefly, 3 ml of the samples were collected in EDTA tubes between 8 AM and 10 AM. After collection of the sample, they were adequately mixed and 50 µl of patient's samples were added into each of the reagent tubes, incubated at room temperature for 60 to 120 minutes. Following this, 50 µl of fixative solution was added and the reading was taken in the instrument with FACS count CD-3 / CD-4 SW, version 1.0 software. Appropriate quality control with previous days' low count, high count and commercially available stabilised blood samples were also carried out on each day.

Detection of HCV – Ab was done using a 3rd generation enzyme-linked immunosorbent assay (ELISA) (UBI HCV EIA 4.0) and /or AXSYM (HCV version 3.0). Results were deduced based on cut-off absorbance value calculated for each

ELISA run. All sample above the cut-off absorbance value were considered positive by ELISA. The signal: cut-off ratio (S/CO) was calculated automatically by the AXSYM. Sample with a ratio of >1.0 were considered to be positive by AXSYM as per the manufacturer's instruction.

Liver function parameters were estimated using IFCC approved method. Transaminases (AST & ALT) methods were an adaptation of the recommended procedure of the IFCC as described by Bergmeyer.

Haemoglobin and platelet counts were estimated from EDTA blood samples using an automated haematology analyser.

Records of all blood investigations are maintained in the electronic medical records which can be viewed only by authorised medical personnel. All records were tabulated to calculate the modified VACS index from an online calculator.(53) The mortality rate for 5 years is automatically calculated at the time of score generation. This would aid in predicting mortality in case of extending the duration of the study.

6. RESULTS

The time period for recruitment of patients for our study extended from 1st June 2012 and extended until 31st May 2013. All patients who were initiated on ART during this period were detected from the registry maintained at the ACTFID ART centre of our institution. Patients were retrospectively recruited into our study after informed consent. They were then actively followed up for a period of 2 years extending from 1st June 2013 to 31st May 2015. At the end of the study period, the outcomes were tabulated to detect associations with individual variables and the modified VACS index.

A total of 251 patients were recruited into the study at the end of the study period. The baseline characteristics of the individuals in the population are as given below:

6.1 BASELINE CHARACTERISTICS

The baseline characteristics of our study cohort are as listed below in the table. On further analysing the baseline characteristics, it can be seen that the mean age group of the cohort was a middle-aged, male predominant age group. The variables were

divided into two groups - the patients who were later found to be in the 'Unfavourable' outcomes group and the 'Alive' group.

The mean age of the patient in the 'Unfavourable' outcomes group was 39.88 ± 12.93 years as compared to the 'Alive' group in which the mean age was found to be 38.09 (10.98) years. The difference between the mean ages of both the groups was not statistically significant.

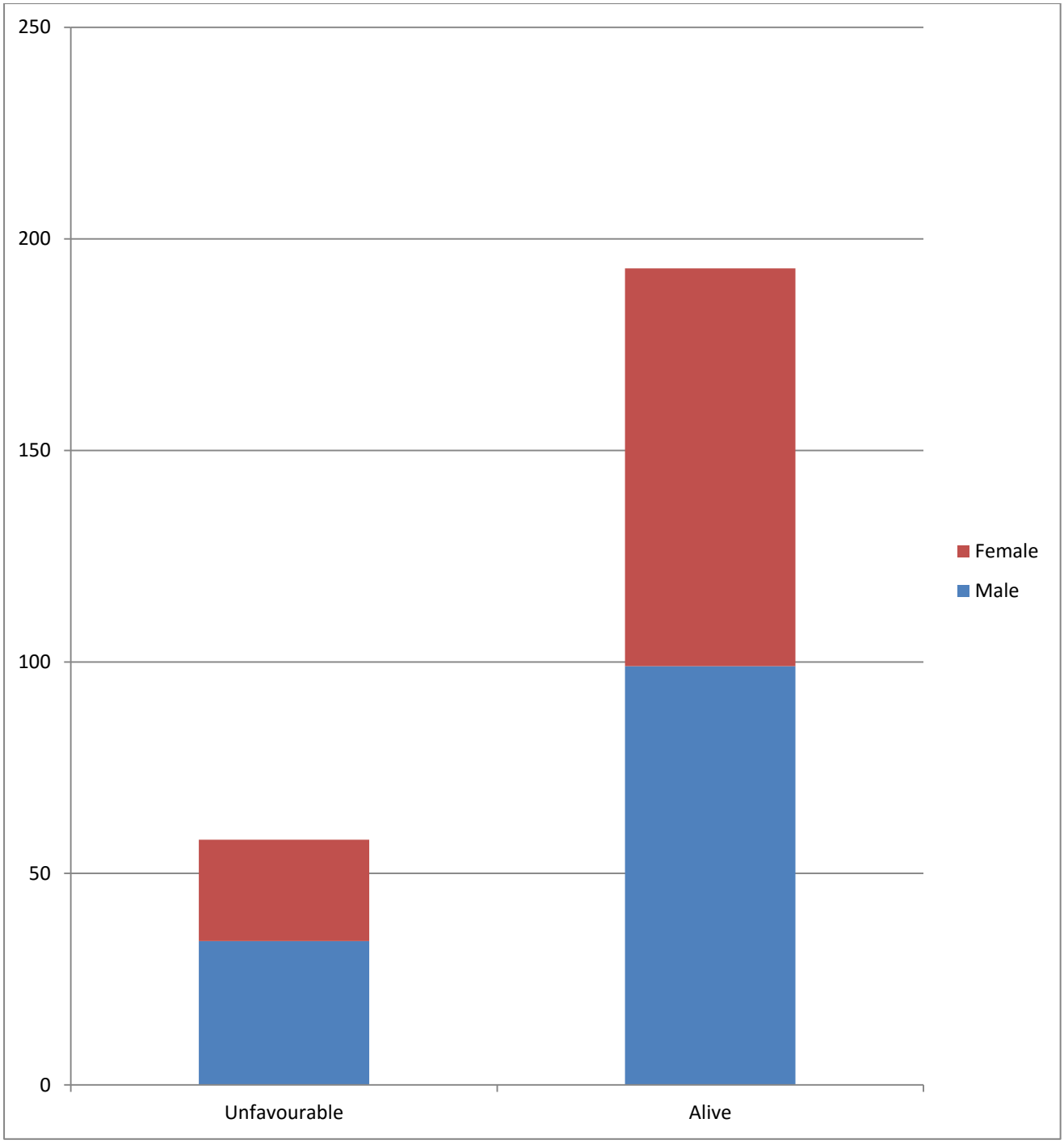


Figure 2. Comparison of Age and Sex in Unfavourable and Alive groups

	Unfavourable 58 (23.1%)		**Alive 193 (76.9%)**		
Variables	**n**	**Median (IQR)**	**n**	**Median (IQR)**	**P value***
CD4	58	140.50 (46.00,270.50)	193	258.00 (146.50,354.00)	.000
Hb	58	11.00 (9.90,12.83)	189	12.00 (10.40,13.65)	.075
AST	52	31.50 (21.00,54.00)	154	26.00 (19.00,45.25)	.150
ALT	54	19.50 (11.00,29.50)	184	15.00 (11.25,28.75)	.290
Platelets	49	225.00 (163.50,267.00)	143	207.00 (163.00,258.00)	.547
FIB4	48	1.29 (0.99,2.13)	131	1.21 (0.80,2.18)	.446
Creatinine(mg/dl)	53	1.02 (0.88,1.16)	190	0.96 (0.80,1.12)	.141
Creatinine(mmol/l)	53	90.17 (77.35,102.99)	190	84.86 (70.72,99.23)	.142
eGFR	51	76.00 (67.00,88.00)	181	80.00 (69.00,91.00)	.322
Age: mean(sd)	58	39.88 (12.93)	193	38.09 (10.98)	0.298[#]
Sex: n(%)					
Female	24 (20.3)		94 (79.7)		0.327[$]
Male	34 (25.6)		99 (74.4)		
HCV: n(%)					
Positive	0 (0)		1 (100.0)		1.000[@]
Negative	45 (26.5)		125 (73.5)		

Table 3. Baseline characteristics of the Unfavourable and Alive groups

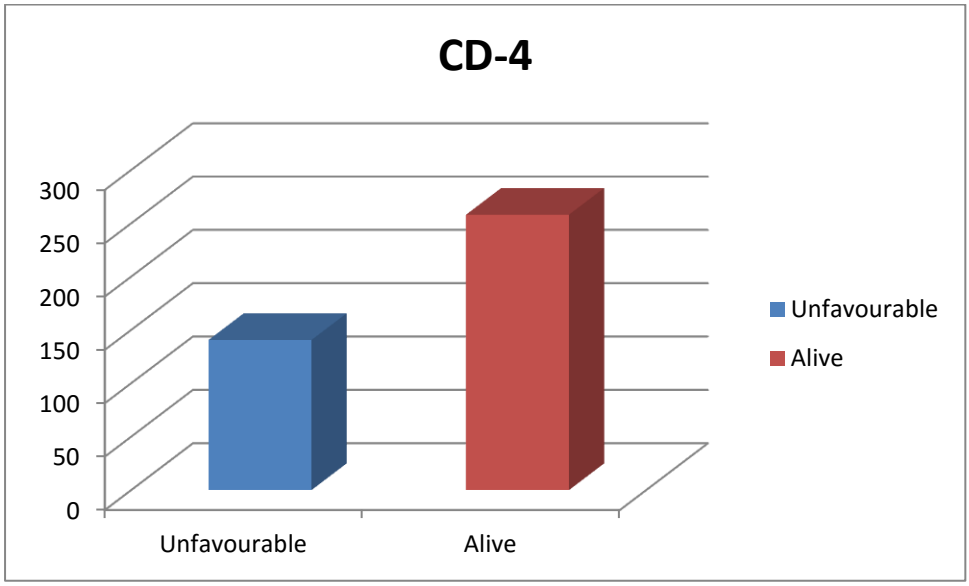
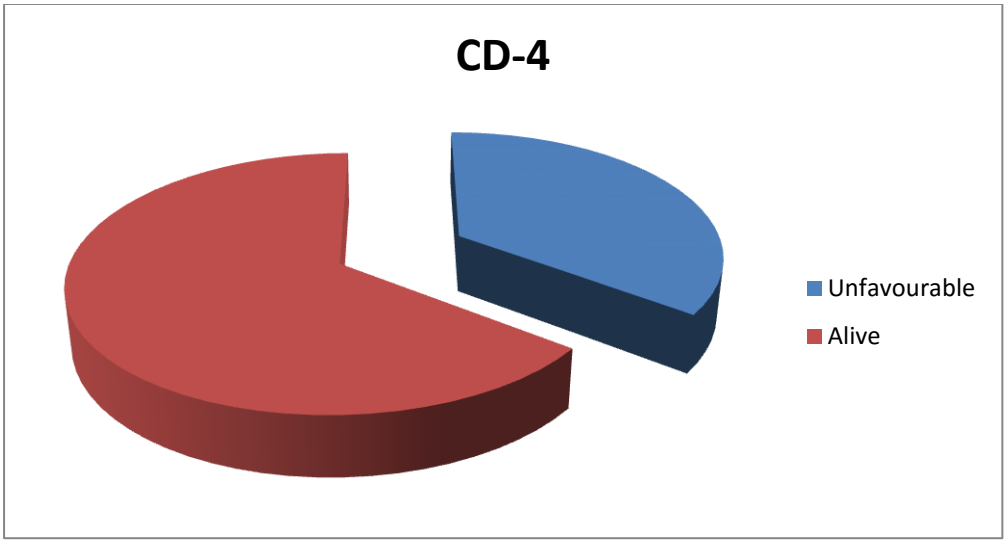


Figure 4.Comparison of CD-4 in Unfavourable and Alive groups



The mean CD – 4 cell count in the ‘Unfavourable’ outcomes group was 140.50 cells /µL (IQR = 46.00 - 270.50) as compared to 258.00 cells /µL (IQR=146.50 - 354.00) in the ‘Alive’ group. The difference between the two groups was statistically significant (P-value=0.000).

There was only a single patient who tested positive for HCV but this patient was present in the ‘Alive’ group. There was no significant difference between AST, ALT, Platelets counts, creatinine, eGFR or FIB-4 between both the groups.

The haemoglobin levels between both the groups was not statistically very different as displayed by a mean Hb level of 11.00 g/dl (IQR=9.90-12.83) in the ‘Unfavourable’ outcomes group and 12.00 g/dl (IQR=10.40-13.65) in the ‘Alive’ group with a P-value of 0.075.

Each of the baseline characteristics were also grouped as per the stratification of the modified VACS Index. This table (Table4) is also displayed as below :

Table 4. Baseline Characteristics stratified as per VACS Index scoring system

Age	< 50	215
	50 – 65	31
	≥ 65	5
	Total	251 100.0%
CD – 4	≥ 500	28
	200 – 499	118
	100 – 199	51
	50 – 99	23
	< 50	31
	Total	251 100.0%
Haemoglobin	≥ 14	44
	12.0 – 13.9	74
	10.0 – 11.9	78
	< 10.0	51

	Total	247 100.0%
eGFR	≥ 60	213
	45.0 – 59.9	13
	30.0 – 44.9	4
	< 30	2
	Total	232 100.0%
FIB - 4	< 1.45	102
	1.45 – 3.25	54
	> 3.25	23
	Total	179 100.0%
Hepatitis C	Positive	1
	Negative	170
	Total	171 100.0%

At the end of the study period on 31st May 2015, the outcomes of patients were tabulated against the baseline blood parameters and Modified VACS Index (MVI) scores. Each of the baseline blood parameters were analysed individually with the final outcome of the patient to detect association with an unfavourable outcome. The MVI was also analysed with the final outcome to detect an association with an unfavourable outcome.

A receiver operating curve (ROC) was also plotted to detect the discriminant function of the MVI to detect the probability of an unfavourable outcome. The best cut-off value for the predicted probability of an unfavourable outcome was calculated following a logistic regression analysis. This value was compared with the actual mortality at the end of the 2 year study period to find out how well the predicted values correlated with the actual values.

The total number of deaths at the end of the study period was found to be 13 patients, with 45 patients being lost to follow up. For a logistic regression analysis, both the number of deaths and patients who were lost to follow up were put together in a group classified as “Unfavourable Outcomes”. For all the analyses, including the bivariate analysis as well as the logistic regression, this nomenclature was adhered to. Hence, at the end of the study period on 31st May 2015, the total number of patients in the unfavourable outcome group was detected to be 58. The total number of patients confirmed to be alive at the end of the study period was 193.

As mentioned in the above paragraph, each of the individual constituent parameters of the MVI was cross-tabulated with the final outcome using a bivariate analysis. The outcomes which displayed a significant association with an unfavourable outcome were employed for the logistic regression analysis. The Modified VACS Index was also cross tabulated with the outcomes to detect a possible correlation.

6.2 PRIMARY OUTCOME

At the end of the analysis, which was done with the aid of a team of expert statisticians, the MVI scores were studied both in the 'Alive' and 'Unfavourable' outcomes group. The results are as tabulated below:

Table5. The Modified VACS Index scores in Unfavourable and Alive Groups

Outcome	**Number**	**Mean MVI score**	**SD**	**SEM**
Unfavourable (Dead/LFU)	58	44.8103	22.46358	2.94961
Alive	193	31.7306	20.39250	1.46788

On studying the above data, it is evident that there is a difference in the MVI scores of both the groups. The mean MVI score in the **'Alive'** group was **31.7306 ± 20.39250** as compared to **44.8103 ± 22.46358** in the **'Unfavourable'** group.

This difference was found to be significant using an Independent Samples T-Test as displayed in the annexures. This implies that a mean higher score was consistently found in the group with the 'Unfavourable' outcomes as compared to the 'Alive' group which was clinically significant, at the end of a 2 year analysis.

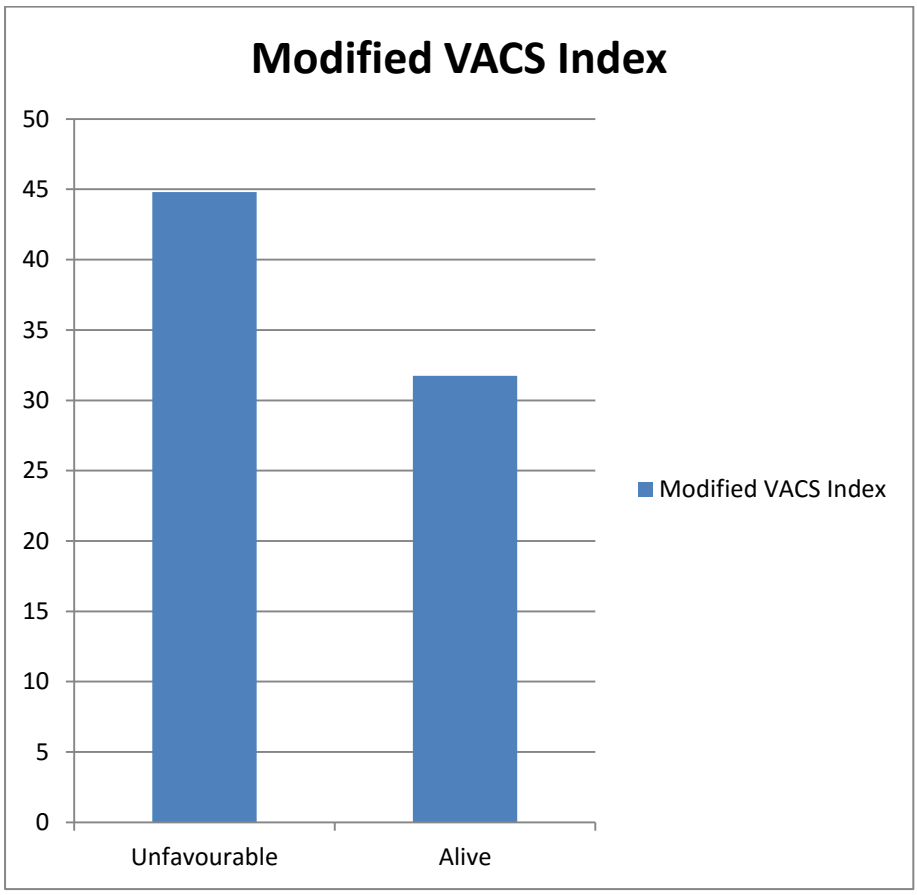
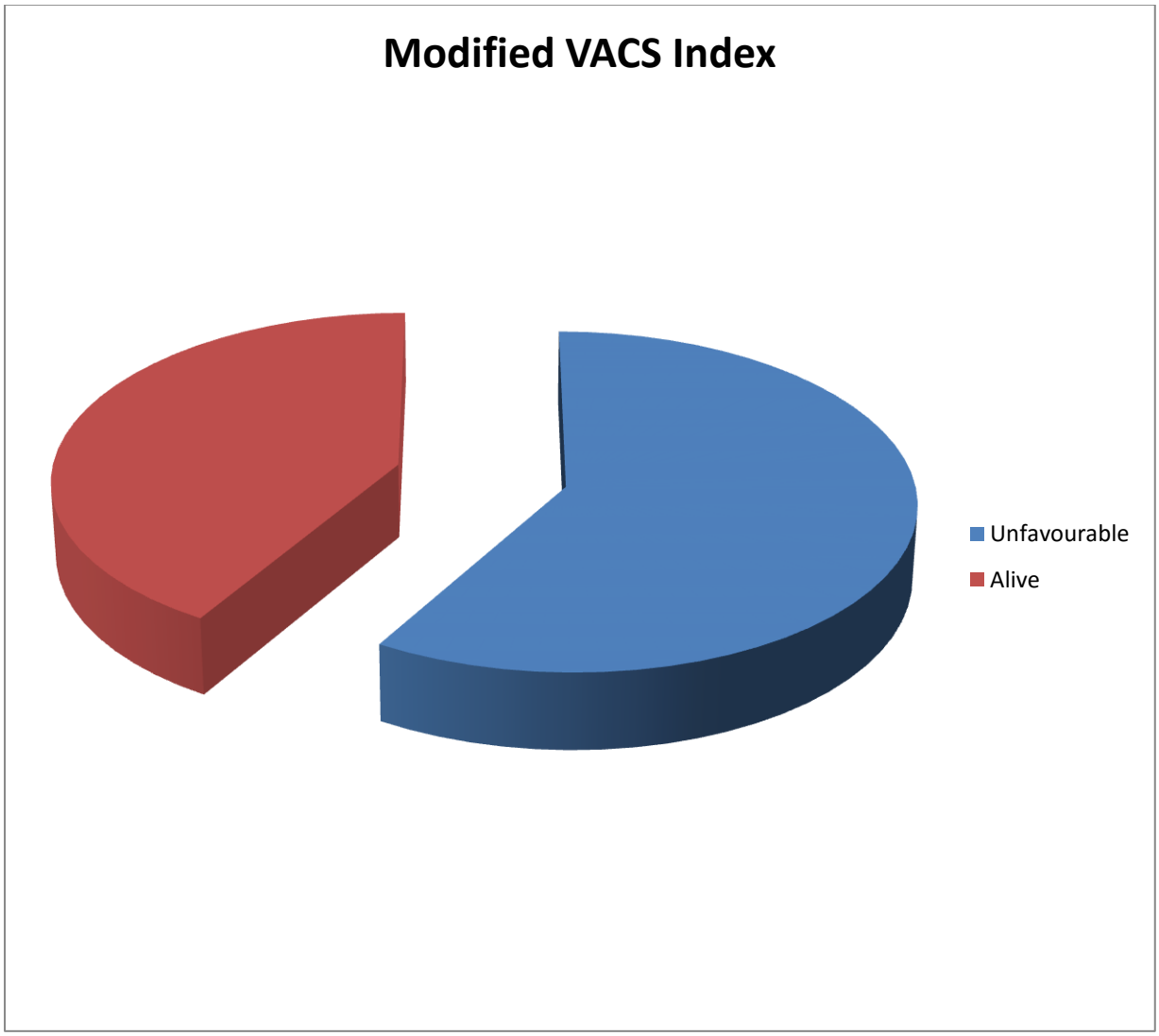


Figure 5a. Comparison of the Modified VACS Index in Unfavourable and Alive groups

Figure 6a. Comparison of the Modified VACS Index in Unfavourable and Alive groups



6.3 SECONDARY OUTCOMES

In the next analysis, an ROC curve was plotted using the data bank derived from the study. For the logistic regression analysis, of all the variables analysed, only CD4 was significantly associated with an adverse outcome. Other variables utilised for the logistic regression analysis were age, creatinine and AST based on the best possible association.

Table6. Variables Employed for Logistic Regression Analysis

	B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
CD-4	.058	.016	12.621	1	.000	1.059	1.026	1.093
Age	.030	.031	.938	1	.333	1.031	.969	1.097
Creatinine	.176	.146	1.457	1	.227	1.192	.896	1.587
AST	.003	.003	1.026	1	.311	1.003	.997	1.008
Constant	-2.295	.362	40.126	1	.000	.101		

In order to find the predictive probability (expected proportion of adverse outcomes), predicted probabilities were computed using the above results. This is like a score ranging from a 0 to 1 scale or 0 to 100%. These were correlated/associated with the outcome.

For the probability value of 0.1845, the sensitivity was found to be 70% and the specificity was found to be 58%. This value of the predicted probability was chosen as the best cut off value and was used to construct the following 2 x 2 table to calculate the validity statistics and the positive predictive values.

Table7. 2X 2 table for construction of ROC Curve

Predicted Status	**Actual Status**		
	Unfavourable	Alive	Total
Unfavourable	35	65	100
Alive	15	88	103
Total	50	153	203

The sensitivity was calculated to be 70% and the specificity was estimated to be 58%. The positive predictive value was calculated to be 35% and the negative predictive value was found to be 85.4%.

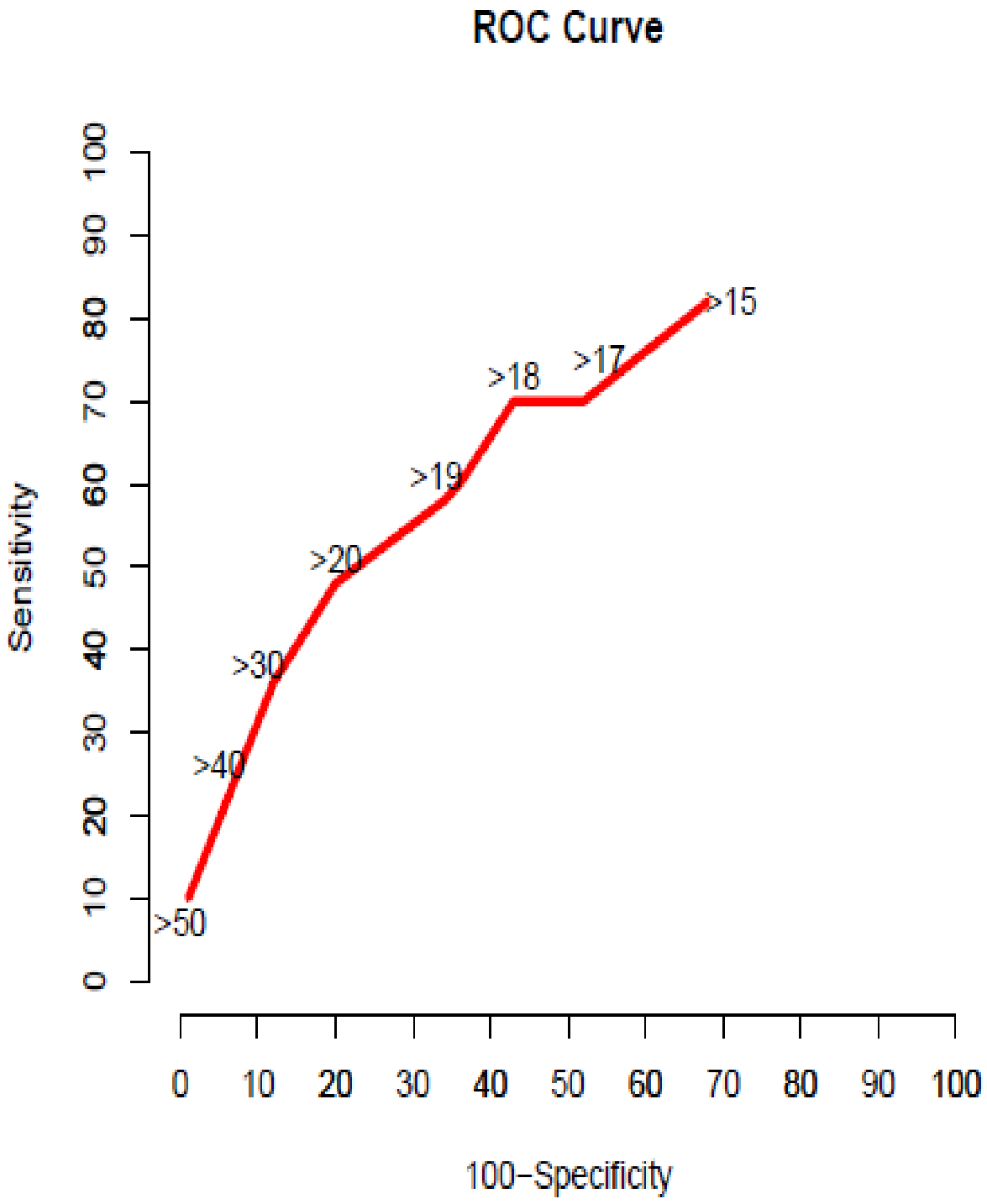


Figure 7. Receiver Operating Curve of the Modified VACS Index

The ROC curve was plotted as shown in the figure above**. The C – statistic of the curve was calculated to be 0.66.** The c statistic conveys how well a model can discriminate between observations at different levels of the outcome. It is the same as the area that lies under the receiver-operating characteristic curve, formed by taking the predicted values from the regression model as a diagnostic test for the event in the data. The minimum value of c is 0.5; the maximum is 1.0. A C-statistic of 0.7 to 0.8 to show acceptable discrimination, values of 0.8 to 0.9 to indicate excellent discrimination, and values of ≥ 0.9 show outstanding discrimination. This implies that the **discriminant function of the modified VACS index is below acceptable discriminant function.**

The **best cut-off of predicted mortality was found to be 0.1845 or 18.45 %.** After 2 years, the total number of confirmed deaths was calculated to be 13; hence, **the actual mortality rate after 2 years was calculated to be 5.17 %.** This implies that **the ratio of the observed to actual mortality would be 28 % (0.28)**, which is **lesser than predicted** by the modified VACS index.

As mentioned previously, of all the constituent baseline parameters of the modified VACS index, only **the CD-4 was found to have a significant association with an unfavourable outcome.**

Table8. CD-4 count of cohort stratified as per VACS scoring system

CD-4 (per cu. mm)	Outcome		Total
	Unfavourable	Alive	
≥ 500	5 (17.9%)	23 (82.1%)	28 (100.0%)
200 – 499	18 (15.3%)	100 (84.7%)	118 (100.0%)
100 – 199	11 (21.6%)	40 (78.4%)	51 (100.0%)
50 – 99	8 (34.8%)	15 (65.2%)	23 (100.0%)
< 50	16 (51.6%)	15 (48.4%)	31 (100.0%)
Total	58 (23.1%)	193 (76.9%)	251 (100.0%)

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	20.539[a]	4	.000
Likelihood Ratio	18.452	4	.001
Linear-by-Linear Association	17.445	1	.000
N of Valid Cases	251		

The significance of the association between CD-4 and adverse outcomes was determined by Chi-Square testing as displayed in the table above.

None of the other individual constituent variables or the composite markers (eGFR and FIB-4) showed a significant correlation with adverse outcomes. This was demonstrated by Chi-Square testing in case of age, haemoglobin, eGFR and FIB-4. Scatter plots and independent samples T-testing was done for detecting associations between AST, ALT, platelets and creatinine and adverse outcomes.

7. DISCUSSION

At the end of a two year follow up of a cohort of patients of diverse age groups with an underlying HIV infection and initiated on ART, we found that there was a significant difference in the Modified VACS Index (MVI) Scores between the patients who were alive and the patients in the 'Unfavourable' outcome group which was a composite of death and patients who were lost to follow up at the end of a two year follow up period.

But, the discriminant function of the MVI score as a prognostic score is not optimal as explained by a ROC curve with a c-statistic of 0.66. The sensitivity of the MVI was calculated to be 70% and the specificity was estimated to be 58%. The positive predictive value was determined to be 35% and the negative predictive value was found to be 85.4%. The predicted mortality was found to be higher than the observed mortality at the culmination of the study period. This may be attributed to better compliance with anti-retroviral therapy with optimum monitoring for side effects of therapy.

The differences in a Western population in which the original VACS Index was validated, and an Indian population, include risk factors, age group at risk and causes of mortality. In an Indian population which has predominantly opportunistic infections, drug toxicity and complications like IRIS as the causes of mortality, a

variable like HCV infection does not act as a precise indicator of morbidity and mortality in the generalised population. In addition, the index does not take into account the type of ART the patient has been initiated on, underlying cardiovascular risk factors, sequelae of previous opportunistic infections, nutritional status and socio-economic status, all of which act as potent barriers in assessing prognosis in PLHIV.

We had a total of 13 deaths and 45 patients lost to follow up after a two year study period. If we take into account all the documented deaths in our cohort over a two year span, we find varied causes of death in these patients. The causes of mortality in all 13 patients who died are as tabulated in Table 9:

Table9. Causes of mortality in all confirmed deaths

Serial No.	Cause of death
Patient 1	• WHO CLINICAL STAGE IV - Clinical and immunological failure to 1st line ART. • Disseminated Tuberculosis
Patient 29	• Decompensated chronic liver disease – Ethanol related • Bacterial peritonitis • Septic shock
Patient 30	• WHO Clinical Stage-IV • Hepatitis B Co-infection • Disseminated TB • Anaemia of Chronic Disease • Chronic Liver Disease-Ascites
Patient 31	• WHO Clinical Stage-IV • Disseminated TB • Oral Candidiasis
Patient 69	• Pulmonary TB in septic shock
Patient 80	• WHO Clinical Stage-IV • Pseudomonas sepsis • Septic shock with multi organ

	dysfunction syndrome (MODS) • Severe neutropenia • Hypokalaemia
Patient 110	• Disseminated TB
Patient 113	• WHO Clinical Stage-IV • TB Meningitis- Communicating hydrocephalus post right ventriculo-peritoneal shunt • Brain stem infarct
Patient 135	• WHO Clinical Stage-IV • Hepatitis B co-infection • Right middle lobe pneumonia • Pulmonary embolism • Zidovudine induced neutropenia
Patient 161	• WHO Clinical Stage-IV • Chronic Diarrhoeal Disease-Cytomegalovirus related • Disseminated Cytomegalovirus Infection
Patient 183	• WHO Clinical Stage-IV • Disseminated TB
Patient 210	• WHO Clinical Stage-IV

	• Disseminated TB
Patient 219	• WHO Clinical Stage-IV • Hodgkin's Lymphoma- STAGE IV B • Type 2 Diabetes Mellitus

As it can be seen from the table, the majority of deaths occurred in severe disease (WHO Clinical Stage-IV). Also, a significant majority of the deaths had an opportunistic infection, which in our community happens to be tuberculosis, which is rampant even amongst individuals whose immunity is quite robust.

Two of the deaths had alcoholic liver disease as an underlying comorbidity. But, the non- inclusion of tuberculosis or opportunistic infections in the index leaves a lacuna in the baseline objective assessment in a PLHIV in an Indian context.

In the original VACS cohort, the study had shown a nearly 20 – fold difference between the estimated 5 year mortality of individuals with a VACS score < 10 as compared to an individual with a VACS score ≥ 60 (5-year mortality of 2.8% as compared to 55% respectively). In the ART-CC study, the difference between the two categories was found to be even more profound (5-year mortality of 1.6% if VACS score < 10 as compared to 41% for a VACS score ≥ 60).

It has to be kept in mind that the original index had the 5-year mortality which was assessed at baseline as compared to our study where the timeline was for 2 years. The study is to be advanced for another 3 years to detect a significant correlation between the modified VACS index and the outcome.

Another major factor which may hinder the discriminant factor of the MVI was the absence of the HIV RNA-PCR which may have added strength to the index. The rationale behind the exclusion of the same was the financial constraints most patients in our hospital settings face in their medical expenses.

8. LIMITATIONS

There were a few limitations of our study which may have impacted the final result. Great care was adopted to limit the possibility of errors in this study. Some of the salient drawbacks are listed below:

- The HIV RNA-PCR was excluded from the modified index as compared to the original index. This may have reduced the discriminant factor of the modified VACS index. This was excluded as the HIV RNA-PCR is an expensive test and is not performed on a routine basis in the ID clinic. The rationale for exclusion of this investigation was to find a good prognostic index correlating with mortality and to be affordable to a patient from a low to middle socio-economic status (SES) which we believe represents the vast majority of patients attending the ID clinic and ACTFID ART centre.

  As compared to the original VACS index which was validated in a cohort of US military veterans which is well funded and supported with a robust health network, our cohort mostly hails from a predominantly lower to middle socio-economic status from a rural backdrop. Knowledge about the HIV pandemic has not yet permeated down to people from remote villages but, awareness amongst the population cohort attending the ID clinic and ART centre

- There were a significant number of patients lost to follow up in our study which may have distorted the outcomes of the study and may have swayed the discriminant factor of the modified VACS index to a less than acceptable c-statistic. This may even affect the study in a way so as to hinder the study of the causes of mortality in patients in whom death was reported as the final outcome.

  Measures were adopted to trace the patients who were lost to follow up by using the contact details mentioned in the hospital records. Home visit workers were employed to trace the missing patients. The missing patients had either emigrated to other places outside the boundary of Tamil Nadu or the address details had changed and had not been updated, hindering our efforts to contact them.

- Another drawback of the study was the fact that our cohort was retrospectively chosen from the time of the study. Our cohort was taken from the time period dating from 1st June 2012 to 31st May 2013. The same cohort was followed up from 1st June 2013 to 31st May 2015. This resulted in a number of missing investigations which may have had an impact on the final results of the study.

The ideal method of conducting the study would have been to prospectively recruit patients but due to the constraints of a limited follow up period if done in such a manner, it was decided to recruit a cohort retrospectively and follow the outcomes after a two year study period. The study can be further extended for a three year duration to match the exact five year mortality with the expected five year outcome as calculated using the modified VACS Index.

Since the investigations we collected were potentially modified after the initiation of ART, hence it was not possible to prospectively collect blood investigations from the date of recruitment for further analysis. These drawbacks will help in formulating a validation study of the MVI in the future in which the sample cohort may be prospectively recruited with ideally no missing blood parameters and potentially new added variables such as tuberculosis or candidiasis at the time of diagnosis. Thresholds for the MVI may need to be redefined for an Indian sample cohort due to regional variations as compared to the original validation cohorts.

9. CONCLUSIONS

From our study, we have seen that the modified VACS Index has a sub-optimal discriminant function to predict mortality after a two year study period in a South Indian HIV infected population who have been initiated on ART. But, the score between the ‘Alive’ and ‘Unfavourable’ outcomes are significantly different; there is a clear demarcation between the scores of both the groups.

The only variable of the MVI which showed a significant association with mortality was the CD-4 count which was employed in the logistic regression to show the predicted mortality after a two year study period.

We recommend extending the study for another three years to compare the predicted five year mortality rate as per the modified VACS index with the actual mortality rate after following up the same cohort of patients.

REFERENCES

1. WHO | Data and statistics [Internet]. [cited 2015 May 11]. Available from: http://www.who.int/hiv/data/en/

2. Annual Report Cover design approved A - NACO_English 2013-14.pdf [Internet]. [cited 2015 May 11]. Available from: http://naco.gov.in/upload/2014%20mslns/NACO_English%202013-14.pdf

3. Antiretroviral therapy in Indian setting: when & what to start with, when & what to switch to? - PubMed - NCBI [Internet]. [cited 2015 May 11]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22310814

4. Operational guidelines for ART services.pdf [Internet]. [cited 2015 May 13]. Available from: http://www.naco.gov.in/upload/Publication/Treatment%20Care%20and%20support/Operational%20guidelines%20for%20ART%20services.pdf

5. Tate JP, Justice AC, Hughes MD, Bonnet F, Reiss P, Mocroft A, et al. An internationally generalizable risk index for mortality after one year of antiretroviral therapy. AIDS Lond Engl. 2013;27(4):563.

6. Neuhaus J. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. - PubMed - NCBI [Internet]. [cited 2015 May 11]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20446848

7. Does an Index Composed of Clinical Data Reflect Effects of Inflammation, Coagulation, and Monocyte Activation on Mortality Among Those Aging With HIV? [Internet]. [cited 2015 Jun 2]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3297653/

8. Origins of HIV and the AIDS Pandemic [Internet]. [cited 2015 May 15]. Available from: http://perspectivesinmedicine.cshlp.org/content/1/1/a006841.full

9. REGION A. INTERIM WHO. [cited 2015 Jul 8]; Available from: http://www.who.int/entity/hiv/pub/guidelines/clinicalstaging.pdf?ua=1

10. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). - PubMed - NCBI [Internet]. [cited 2015 May 13]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6189183

11. The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex — NEJM [Internet]. [cited 2015 May 13]. Available from: http://www.nejm.org/doi/full/10.1056/NEJM198707233170401

12. Combination therapy with zidovudine and dideoxycytidine in patients with advanced human immunodeficiency virus infection. A phase I/II study. - PubMed - NCBI [Internet]. [cited 2015 May 13]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1345755

13. Evidence for HTLV-III infection in prostitutes in Tamil Nadu (India). - PubMed - NCBI [Internet]. [cited 2015 May 13]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3623641

14. :: National Health Mission – Tamil Nadu :: [Internet]. [cited 2015 May 13]. Available from: http://www.nrhmtn.gov.in/statglance.html

15. Census 2011 - census2011_tn.pdf [Internet]. [cited 2015 May 13]. Available from: http://www.census.tn.nic.in/whatsnew/census2011_tn.pdf

16. STATE HIV EPIDEMIC FACT SHEET.pdf [Internet]. [cited 2015 May 13]. Available from: http://naco.gov.in/upload/2014%20mslns/STATE%20HIV%20EPIDEMIC%20FACT%20SHEET.pdf

17. Wester CW, Okezie OA, Thomas AM, Bussmann H, Moyo S, Muzenda T, et al. Higher-than-expected rates of lactic acidosis among highly active antiretroviral therapy-treated women in Botswana: preliminary results from a large randomized clinical trial. J Acquir Immune Defic Syndr 1999. 2007 Nov 1;46(3):318–22.

18. Bolhaar MG, Karstaedt AS. A high incidence of lactic acidosis and symptomatic hyperlactatemia in women receiving highly active antiretroviral therapy in Soweto, South Africa. Clin Infect Dis Off Publ Infect Dis Soc Am. 2007 Jul 15;45(2):254–60.

19. Manosuthi W, Prasithsirikul W, Chumpathat N, Suntisuklappon B, Athichathanabadi C, Chimsuntorn S, et al. Risk factors for mortality in symptomatic hyperlactatemia among HIV-infected patients receiving antiretroviral therapy in a resource-limited setting. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2008 Nov;12(6):582–6.

20. Reisler RB, Murphy RL, Redfield RR, Parker RA. Incidence of pancreatitis in HIV-1-infected individuals enrolled in 20 adult AIDS clinical trials group studies: lessons learned. J Acquir Immune Defic Syndr 1999. 2005 Jun 1;39(2):159–66.

21. Forna F, Liechty CA, Solberg P, Asiimwe F, Were W, Mermin J, et al. Clinical toxicity of highly active antiretroviral therapy in a home-based AIDS care program in rural Uganda. J Acquir Immune Defic Syndr 1999. 2007 Apr 1;44(4):456–62.

22. Martínez E, Milinkovic A, de Lazzari E, Ravasi G, Blanco JL, Larrousse M, et al. Pancreatic toxic effects associated with co-administration of didanosine and tenofovir in HIV-infected adults. Lancet Lond Engl. 2004 Jul 3;364(9428):65–7.

23. Ait-Mohand H, Bonmarchand M, Guiguet M, Slama L, Marguet F, Behin A, et al. Viral efficacy maintained and safety parameters improved with a reduced dose of stavudine: a pilot study. HIV Med. 2008 Oct;9(9):738–46.

24. Kumarasamy N, Venkatesh KK, Cecelia AJ, Devaleenal B, Lai AR, Saghayam S, et al. Spectrum of adverse events after generic HAART in southern Indian HIV-infected patients. AIDS Patient Care STDs. 2008 Apr;22(4):337–44.

25. Hawkins C, Achenbach C, Fryda W, Ngare D, Murphy R. Antiretroviral durability and tolerability in HIV-infected adults living in urban Kenya. J Acquir Immune Defic Syndr 1999. 2007 Jul 1;45(3):304–10.

26. Sacktor N, Nakasujja N, Skolasky RL, Robertson K, Musisi S, Ronald A, et al. Benefits and risks of stavudine therapy for HIV-associated neurologic complications in Uganda. Neurology. 2009 Jan 13;72(2):165–70.

27. Mehta SA, Ahmed A, Laverty M, Holzman RS, Valentine F, Sivapalasingam S. Sex differences in the incidence of peripheral neuropathy among Kenyans initiating antiretroviral therapy. Clin Infect Dis Off Publ Infect Dis Soc Am. 2011 Sep;53(5):490–6.

28. Microsoft Word - WHO-Guidelines-Low dose d4T technical - Note for web _Final2_.doc - ARTadultsaddendum.pdf [Internet]. [cited 2015 Sep 6]. Available from: http://www.who.int/hiv/art/ARTadultsaddendum.pdf

29. Gerschenson M, Kim C, Berzins B, Taiwo B, Libutti DE, Choi J, et al. Mitochondrial function, morphology and metabolic parameters improve after switching from stavudine to a tenofovir-containing regimen. J Antimicrob Chemother. 2009 Jun;63(6):1244–50.

30. Haas DW, Ribaudo HJ, Kim RB, Tierney C, Wilkinson GR, Gulick RM, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS Lond Engl. 2004 Dec 3;18(18):2391–400.

31. Cohen K, Grant A, Dandara C, McIlleron H, Pemba L, Fielding K, et al. Effect of rifampicin-based antitubercular therapy and the cytochrome P450 2B6 516G>T polymorphism on efavirenz concentrations in adults in South Africa. Antivir Ther. 2009;14(5):687–95.

32. Renaud-Théry F, Nguimfack BD, Vitoria M, Lee E, Graaff P, Samb B, et al. Use of antiretroviral therapy in resource-limited countries in 2006: distribution and

uptake of first- and second-line regimens. AIDS Lond Engl. 2007 Jul;21 Suppl 4:S89–95.

33. Wit FWNM, Kesselring AM, Gras L, Richter C, van der Ende ME, Brinkman K, et al. Discontinuation of nevirapine because of hypersensitivity reactions in patients with prior treatment experience, compared with treatment-naive patients: the ATHENA cohort study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2008 Mar 15;46(6):933–40.

34. Dart Trial Team. Twenty-four-week safety and tolerability of nevirapine vs. abacavir in combination with zidovudine/lamivudine as first-line antiretroviral therapy: a randomized double-blind trial (NORA). Trop Med Int Health TM IH. 2008 Jan;13(1):6–16.

35. Reid A, Stöhr W, Walker AS, Williams IG, Kityo C, Hughes P, et al. Severe renal dysfunction and risk factors associated with renal impairment in HIV-infected adults in Africa initiating antiretroviral therapy. Clin Infect Dis Off Publ Infect Dis Soc Am. 2008 Apr 15;46(8):1271–81.

36. Kiertiburanakul S, Sungkanuparph S, Charoenyingwattana A, Mahasirimongkol S, Sura T, Chantratita W. Risk factors for nevirapine-associated rash among HIV-infected patients with low CD4 cell counts in resource-limited settings. Curr HIV Res. 2008 Jan;6(1):65–9.

37. Rao N, White GJ. Successful treatment of Enterococcus faecalis prosthetic valve endocarditis with linezolid. Clin Infect Dis Off Publ Infect Dis Soc Am. 2002 Oct 1;35(7):902–4.

38. Mutimura E, Stewart A, Rheeder P, Crowther NJ. Metabolic function and the prevalence of lipodystrophy in a population of HIV-infected African subjects receiving highly active antiretroviral therapy. J Acquir Immune Defic Syndr 1999. 2007 Dec 1;46(4):451–5.

39. Buchacz K, Weidle PJ, Moore D, Were W, Mermin J, Downing R, et al. Changes in lipid profile over 24 months among adults on first-line highly active antiretroviral therapy in the home-based AIDS care program in rural Uganda. J Acquir Immune Defic Syndr 1999. 2008 Mar 1;47(3):304–11.

40. fs310_2008.pdf [Internet]. [cited 2015 Sep 6]. Available from: http://www.who.int/mediacentre/factsheets/fs310_2008.pdf

41. Vorster HH, Venter CS, Wissing MP, Margetts BM. The nutrition and health transition in the North West Province of South Africa: a review of the THUSA (Transition and Health during Urbanisation of South Africans) study. Public Health Nutr. 2005 Aug;8(5):480–90.

42. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis. 2010 Feb 1;201(3):318–30.

43. Nebié Y, Meda N, Leroy V, Mandelbrot L, Yaro S, Sombié I, et al. Sexual and reproductive life of women informed of their HIV seropositivity: a prospective cohort study in Burkina Faso. J Acquir Immune Defic Syndr 1999. 2001 Dec 1;28(4):367–72.

44. DeSimone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1-infected persons after initiation of highly active antiretroviral therapy. Ann Intern Med. 2000 Sep 19;133(6):447–54.

45. French MA. HIV/AIDS: immune reconstitution inflammatory syndrome: a reappraisal. Clin Infect Dis Off Publ Infect Dis Soc Am. 2009 Jan 1;48(1):101–7.

46. Murdoch DM, Venter WDF, Feldman C, Van Rie A. Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. AIDS Lond Engl. 2008 Mar 12;22(5):601–10.

47. Sandler NG, Wand H, Roque A, Law M, Nason MC, Nixon DE, et al. Plasma Levels of Soluble CD14 Independently Predict Mortality in HIV Infection. J Infect Dis. 2011 Mar 15;203(6):780–90.

48. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. Ann Intern Med. 1999;130(6):515–24.

49. Veterans Aging Cohort Study (VACS) [Internet]. [cited 2015 Jun 2]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3049942/

50. Towards a combined prognostic index for survival in HIV infection: the role of “non-HIV” biomarkers [Internet]. [cited 2015 Jun 2]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3077949/

51. JAMA Network | JAMA Internal Medicine | The Changing Incidence of AIDS Events in Patients Receiving Highly Active Antiretroviral Therapy [Internet]. [cited 2015 Jun 2]. Available from: http://archinte.jamanetwork.com/article.aspx?articleid=486426

52. Antiretroviral Therapy Cohort Collaboration (ART-CC). Variable Impact on Mortality of AIDS-Defining Events Diagnosed during Combination Antiretroviral Therapy: Not All AIDS-Defining Conditions Are Created Equal. Clin Infect Dis. 2009 Apr 15;48(8):1138–51.

53. VACS Index Information and VACS Index Calculator > Veterans Aging Cohort Study | Internal Medicine | Yale School of Medicine [Internet]. [cited 2015 May 12]. Available from: http://www.vacohort.org/welcome/vacsindexinfo.aspx

54. CHRISTIAN MEDICAL COLLEGE - fhivmedpros.pdf [Internet]. [cited 2015 Jun 26]. Available from: http://www.cmch-vellore.edu/pdf/fhivmedpros.pdf

ANNEXURES

Annexure-1 :STATISTICAL ANALYSIS

Some list of data to check the Coding:

slno	age_V	CD4_V	hb_V	egfr_v	fib4_V	score1	outcome_new
1.00	.00	29.00	38.00	.00	6.00	73.00	1.00
2.00	.00	10.00	38.00	.00	.00	48.00	2.00
3.00	12.00	6.00	38.00	26.00	.00	82.00	1.00
4.00	.00	10.00	38.00	.00	.00	48.00	2.00
5.00	.00	6.00	22.00	.00	.00	28.00	2.00
6.00	.00	28.00	10.00	.00	.00	38.00	2.00

Cross tabulations with outcome (Alive vs others).

age_V * outcome_new

Crosstab

			outcome_new		Total
			Dead	Alive	
age_V	.00	Count	47	168	215
		% within age_V	21.9%	78.1%	100.0%
	12.00	Count	9	22	31
		% within age_V	29.0%	71.0%	100.0%
	27.00	Count	2	3	5
		% within age_V	40.0%	60.0%	100.0%
Total		Count	58	193	251
		% within age_V	23.1%	76.9%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.604[a]	2	.449
Likelihood Ratio	1.478	2	.478
Linear-by-Linear Association	1.591	1	.207
N of Valid Cases	251		

a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is 1.16.

CD4_V * outcome_new

Crosstab

			outcome_new		Total
			Dead	Alive	
CD4_V	.00	Count	5	23	28
		% within CD4_V	17.9%	82.1%	100.0%
	6.00	Count	18	100	118
		% within CD4_V	15.3%	84.7%	100.0%
	10.00	Count	11	40	51
		% within CD4_V	21.6%	78.4%	100.0%
	28.00	Count	8	15	23
		% within CD4_V	34.8%	65.2%	100.0%
	29.00	Count	16	15	31
		% within CD4_V	51.6%	48.4%	100.0%
Total		Count	58	193	251
		% within CD4_V	23.1%	76.9%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	20.539[a]	4	.000
Likelihood Ratio	18.452	4	.001
Linear-by-Linear Association	17.445	1	.000
N of Valid Cases	251		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 5.31.

hb_V * outcome_new

Crosstab

			outcome_new		Total
			Dead	Alive	
hb_V	.00	Count	5	39	44
		% within hb_V	11.4%	88.6%	100.0%
	10.00	Count	18	56	74
		% within hb_V	24.3%	75.7%	100.0%
	22.00	Count	19	59	78
		% within hb_V	24.4%	75.6%	100.0%
	38.00	Count	16	35	51
		% within hb_V	31.4%	68.6%	100.0%
Total		Count	58	189	247
		% within hb_V	23.5%	76.5%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5.426[a]	3	.143
Likelihood Ratio	5.923	3	.115
Linear-by-Linear Association	4.141	1	.042
N of Valid Cases	247		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 10.33.

egfr_v * outcome_new

Crosstab

	outcome_new		Total
	Dead	Alive	

egfr_v	.00	Count	44	169	213
		% within egfr_v	20.7%	79.3%	100.0%
	6.00	Count	4	9	13
		% within egfr_v	30.8%	69.2%	100.0%
	8.00	Count	2	2	4
		% within egfr_v	50.0%	50.0%	100.0%
	26.00	Count	1	1	2
		% within egfr_v	50.0%	50.0%	100.0%
Total		Count	51	181	232
		% within egfr_v	22.0%	78.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3.550[a]	3	.314
Likelihood Ratio	3.022	3	.388
Linear-by-Linear Association	2.731	1	.098
N of Valid Cases	232		

a. 5 cells (62.5%) have expected count less than 5. The minimum expected count is .44.

fib4_V * outcome_new

Crosstab

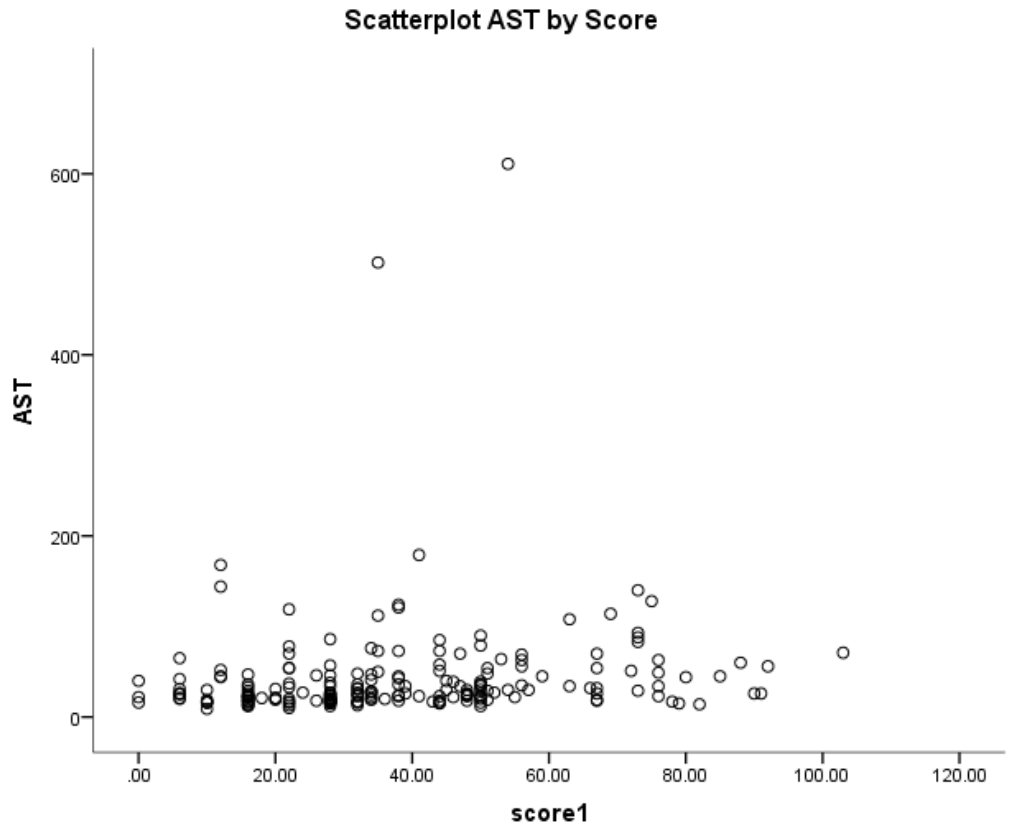
			outcome_new		Total
			Dead	Alive	
fib4_V	.00	Count	27	75	102
		% within fib4_V	26.5%	73.5%	100.0%
	6.00	Count	14	40	54
		% within fib4_V	25.9%	74.1%	100.0%
	25.00	Count	7	16	23
		% within fib4_V	30.4%	69.6%	100.0%
Total		Count	48	131	179
		% within fib4_V	26.8%	73.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.181[a]	2	.913
Likelihood Ratio	.178	2	.915
Linear-by-Linear Association	.138	1	.710
N of Valid Cases	179		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 6.17.

AST and Score:




```
t-test   groups = outcome_new(1,2) / variables =  AST / criteria = ci(.95).
```

T-Test

```
[DataSet1] C:\JEY\Medicine\Adithya\Adhitya_29Jun15.sav
```

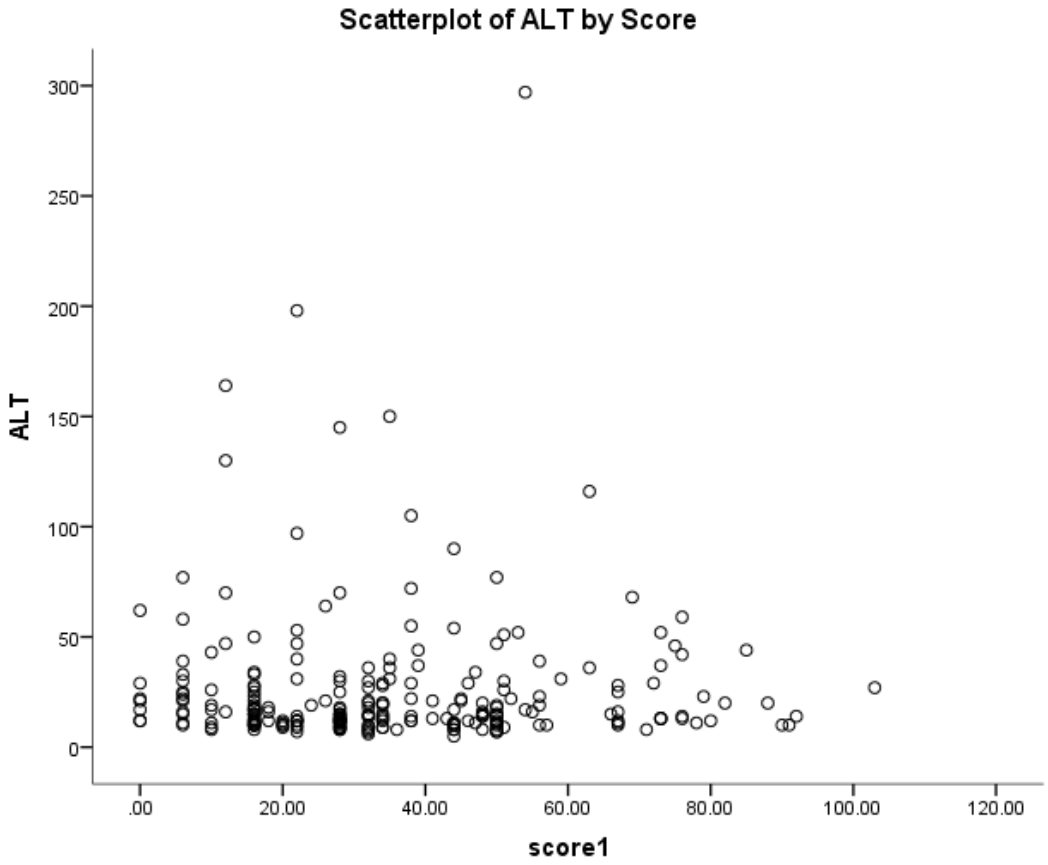
Group Statistics

	outcome_new	N	Mean	Std. Deviation	Std. Error Mean
AST	Dead	52	53.33	84.874	11.770
	Alive	154	39.95	47.162	3.800

Independent Samples Test

		Levene's Test for Equality of Variances				
		F	Sig.	t	df	Sig. (2-tailed)
AST	Equal variances assumed	2.852	.093	1.416	204	.158
	Equal variances not assumed			1.082	61.964	.284

ALT and Score:




```
t-test groups = outcome_new(1,2) / variables = ALT / criteria = ci(.95).
```

T-Test

```
[DataSet1] C:\JEY\Medicine\Adithya\Adhitya_29Jun15.sav
```

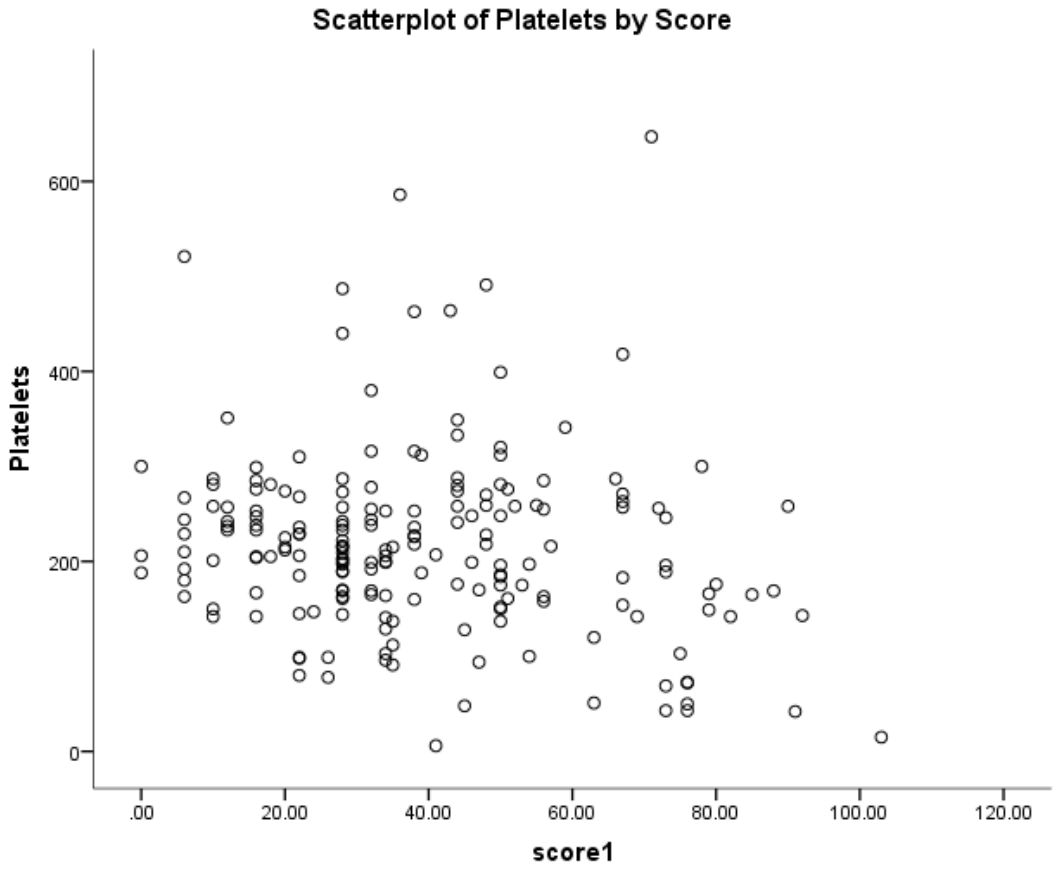
Group Statistics

	outcome_new	N	Mean	Std. Deviation	Std. Error Mean
ALT	Dead	54	28.30	40.104	5.457
	Alive	184	26.03	29.220	2.154

Independent Samples Test

		Levene's Test for Equality of Variances				
		F	Sig.	t	df	Sig. (2-tailed)
ALT	Equal variances assumed	.001	.977	.458	236	.647
	Equal variances not assumed			.387	70.307	.700

Platelets and Score:




```
t-test   groups = outcome_new(1,2) / variables = Platelets / criteria = ci(.95).
```

T-Test

```
[DataSet1] C:\JEY\Medicine\Adithya\Adhitya_29Jun15.sav
```

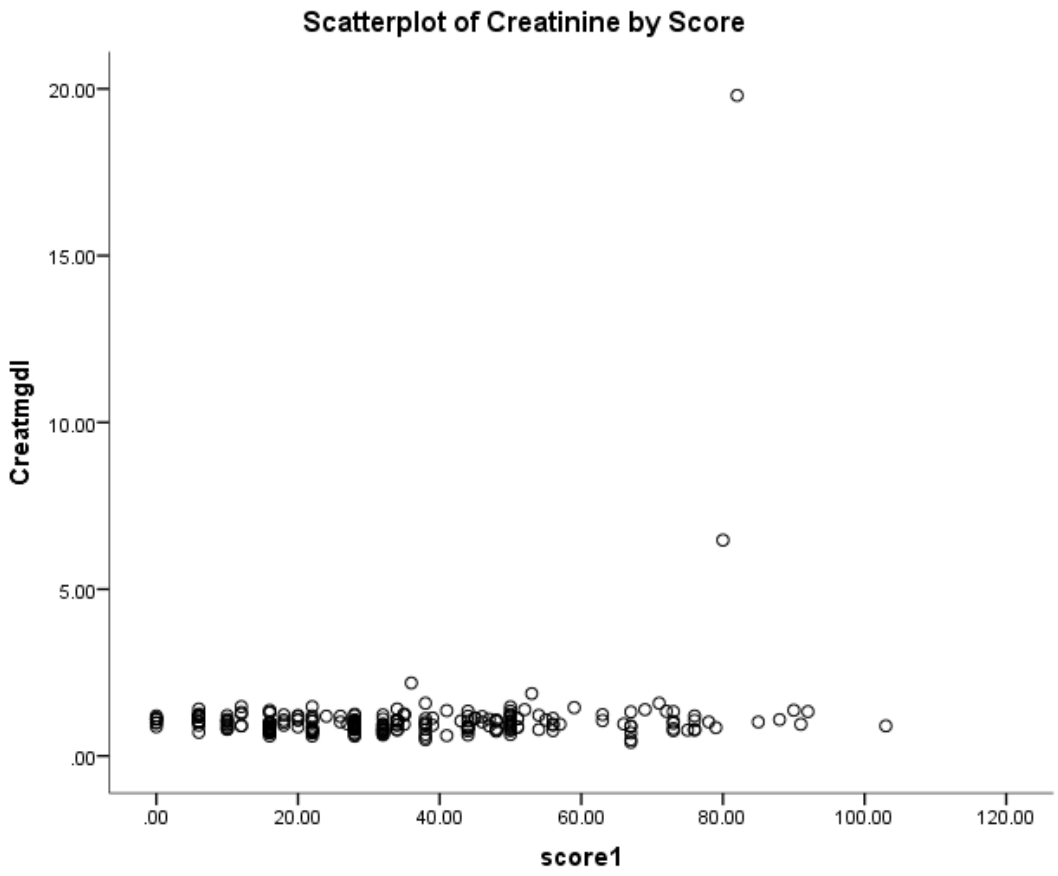
Group Statistics

	outcome_new	N	Mean	Std. Deviation	Std. Error Mean
Platelets	Dead	49	222.35	96.605	13.801
	Alive	143	215.98	96.282	8.052

Independent Samples Test

		Levene's Test for Equality of Variances				
		F	Sig.	t	df	Sig. (2-tail
Platelets	Equal variances assumed	.155	.694	.399	190	.690
	Equal variances not assumed			.399	82.987	.691

Creatinine (mg/dl) and Score :



It appears as though there are couple of outliers. However, no correlation.

```
t-test groups = outcome_new(1,2) / variables =  Creatmgdl  / criteria = ci(.95).
```

T-Test

```
[DataSet1] C:\JEY\Medicine\Adithya\Adhitya_29Jun15.sav
```

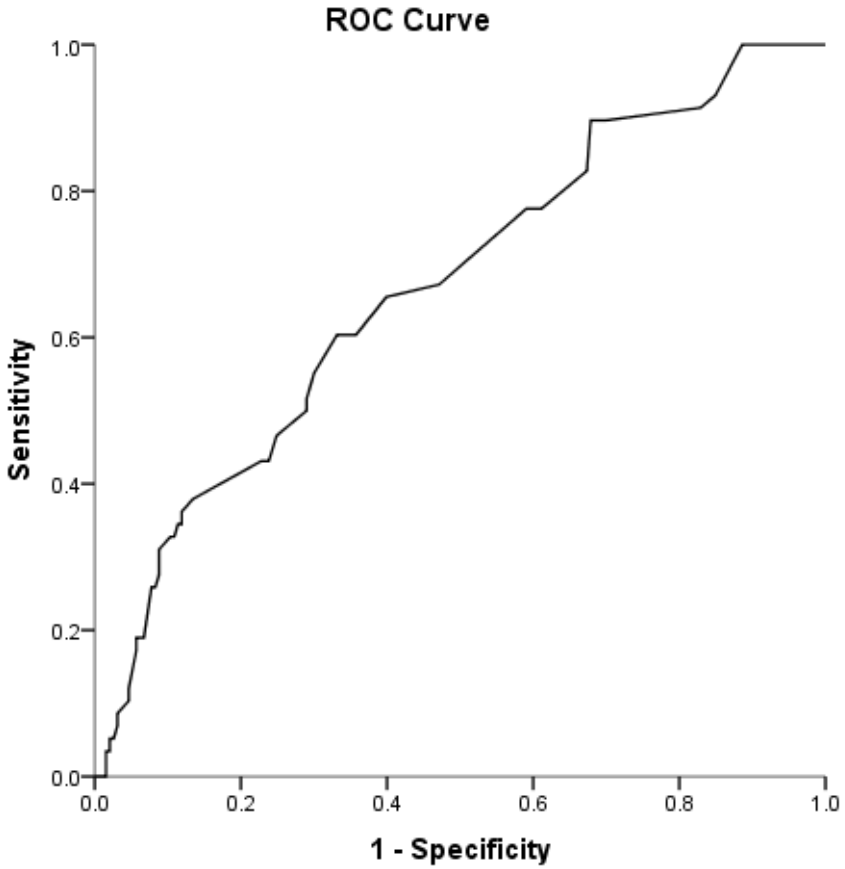
Group Statistics

	outcome_new	N	Mean	Std. Deviation	Std. Error Mean
Creatmgdl	Dead	53	1.3715	2.59104	.35591
	Alive	190	1.0089	.46227	.03354

Independent Samples Test

		Levene's Test for Equality of Variances				
		F	Sig.	t	df	Sig. (2-tailed
Creatmgdl	Equal variances assumed	7.047	.008	1.836	241	.068
	Equal variances not assumed			1.014	52.926	.315

ROC Curve of Score with Outcome (Dead vs Others).



Diagonal segments are produced by ties.

T-Test

Group Statistics

	outcome_new	N	Mean	Std. Deviation	Std. Error Mean
score1	Dead	58	44.8103	22.46358	2.94961
	Alive	193	31.7306	20.39250	1.46788

Independent Samples Test

		Levene's Test for Equality of Variances				
		F	Sig.	t	df	Sig. (2-tailed)
score1	Equal variances assumed	2.596	.108	4.182	249	.000
	Equal variances not assumed			3.970	87.142	.000

Syntax:

```
**** Weights for AGe.
*****  V implies VACS Index.
if  (age <50) age_V=0.
if (age >=50 and age <=64 ) age_V=12.
if (age >=65) age_V=27.
exec.
freq age_v.

* CD4 Weights.
****** VACS weights.

If (cd4 >= 500) CD4_V=0.
if (cd4>=350 and cd4 <=499 )cd4_V=6.
if (cd4>=200 and cd4 <=349 )cd4_V=6.
if (cd4>=100 and cd4 <=199 )cd4_V=10.
if (cd4>=50 and cd4 <=99 )cd4_V=28.
If (cd4 <50) CD4_V=29.
exec.
freq cd4_v.


*******   Hemoglobin.
if (hb >=14) hb_V=0.
if (hb >=12 and hb <= 13.9) hb_v=10.
if (hb >=10 and hb <= 11.9) hb_v=22.
if (hb <10) hb_V=38.
exe.
freq hb_v.
**** .


***** FIB 4.
if (fib4 <1.45) fib4_V=0.
if (fib4 >=1.45 and fib4 <=3.25) fib4_v=6.
if (fib4 >3.25 ) fib4_V =25.
exec.
freq fib4_v.


***** eGFR.
if (egfr >=60) egfr_v =0.
if (egfr >=45 and egfr<=59.9) egfr_v=6.
if (egfr >=30 and egfr <=44.9) egfr_v=8.
if (egfr <30 ) egfr_v=26.
exec.
freq egfr_v.
```

Outcome:

```
if (outcome = "Alive" ) outcome_new =2.
if (outcome = "Death")outcome_new=1.
```

```
if (outcome = "LFU" ) outcome_new =1.
val lab outcome_new  1 "Dead" 2 "Alive".
exec.
freq outcome_new.


compute score1 = sum (age_v, cd4_v, HB_v , egfr_v, fib4_v).
exec.
mean score by outcome_new/ stat= anova .
```

Further analyses to find the Predictive value of a Model:

Note : Death and LFU combined together as bad outcome for the following analyses.

Based on the bi-variate analyses, I have chosen 4 variables. That are: CD4, Creatinine, AST and Age. Though the age was not at all significant (very high p value), due to biological reason this was included. Of these 4 variables, only CD4 is significant. The following is the results of Logistic Regression analysis.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	CD4_V	.058	.016	12.621	1	.000	1.059	1.026	1.093
	age_V	.030	.031	.938	1	.333	1.031	.969	1.097
	Creatmgdl	.176	.146	1.457	1	.227	1.192	.896	1.587
	AST	.003	.003	1.026	1	.311	1.003	.997	1.008
	Constant	-2.295	.362	40.126	1	.000	.101		

a. Variable(s) entered on step 1: CD4_V, age_V, Creatmgdl, AST.

In order to find the predictive probability (expected proportion of bad outcomes), predicted probabilities were computed using the above results. This is like a score ranging from 0 to 1 scale or 0 to 100%. These were correlated/associated with the outcome. The following table presents the predicted probabilities against outcome.

Coordinates of the Curve

Test Result Variable(s):Predicted probability

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
.0000000	1.000	1.000
.1053703	1.000	.993
.1061755	1.000	.987

.1072590	1.000	.980
.1086935	.980	.980
.1098943	.980	.974
.1109311	.960	.974
.1115071	.960	.967
.1134248	.960	.961
.1150867	.960	.954
.1165893	.960	.948
.1195137	.960	.941
.1250367	.960	.935
.1309920	.960	.928
.1385451	.940	.928
.1442989	.940	.922
.1445493	.920	.922
.1447670	.920	.915
.1449521	.920	.908
.1451458	.920	.902
.1452262	.920	.895
.1452881	.920	.889
.1456930	.920	.882
.1462225	.920	.876
.1464901	.920	.869
.1466334	.900	.869
.1467581	.900	.863
.1468641	.900	.856
.1470703	.900	.850
.1473580	.900	.843
.1476085	.900	.837
.1481989	.880	.837
.1486769	.880	.830
.1487235	.860	.830
.1488350	.860	.824
.1489906	.860	.817
.1490979	.860	.810
.1493805	.860	.804
.1496336	.860	.797
.1496718	.840	.797
.1497247	.840	.791
.1498177	.840	.784
.1504287	.840	.778
.1510612	.840	.771
.1513212	.840	.765
.1516693	.840	.758
.1519601	.840	.752
.1521227	.840	.745
.1522169	.840	.739
.1523649	.840	.732
.1525774	.840	.725
.1527212	.840	.719
.1529147	.840	.712
.1532269	.840	.706
.1534252	.840	.699

.1534855	.840	.693
.1537944	.840	.686
.1543528	.820	.686
.1548280	.820	.680
.1552498	.820	.673
.1554610	.820	.667
.1560999	.800	.667
.1570461	.800	.660
.1574155	.780	.660
.1576010	.780	.654
.1580511	.780	.647
.1587041	.760	.647
.1594864	.760	.641
.1599402	.760	.634
.1600318	.760	.627
.1601684	.760	.621
.1605573	.760	.614
.1613064	.760	.608
.1627041	.760	.601
.1637332	.740	.601
.1639014	.740	.595
.1645858	.740	.588
.1659212	.720	.588
.1667162	.720	.582
.1669799	.720	.575
.1676207	.700	.575
.1681636	.700	.569
.1689206	.700	.562
.1697278	.700	.556
.1701706	.700	.549
.1707786	.700	.542
.1712425	.700	.536
.1720964	.700	.529
.1734819	.700	.523
.1748936	.700	.516
.1767523	.700	.510
.1779684	.700	.503
.1783330	.700	.497
.1787543	.700	.490
.1791422	.700	.484
.1794795	.700	.477
.1801389	.700	.471
.1808343	.700	.464
.1813119	.700	.458
.1821610	.700	.451
.1828638	.700	.444
.1831269	.700	.438
.1835325	.700	.431
.1845332	.700	.425
.1853106	.680	.425
.1854537	.680	.418
.1859638	.660	.418

.1866658	.640	.418
.1871780	.620	.418
.1874812	.620	.412
.1877318	.620	.405
.1882161	.620	.399
.1886730	.600	.399
.1889247	.600	.392
.1891256	.600	.386
.1912403	.600	.379
.1935645	.600	.373
.1952873	.600	.366
.1978080	.600	.359
.1990730	.600	.353
.1998274	.600	.346
.2025574	.600	.340
.2053961	.580	.340
.2061782	.580	.333
.2065482	.580	.327
.2082629	.580	.320
.2102411	.580	.314
.2109914	.580	.307
.2114007	.580	.301
.2121242	.580	.294
.2133679	.580	.288
.2144094	.580	.281
.2173867	.580	.275
.2219800	.580	.268
.2261475	.580	.261
.2299274	.580	.255
.2319418	.560	.255
.2343094	.560	.248
.2401359	.560	.242
.2454488	.560	.235
.2473430	.560	.229
.2486437	.560	.222
.2495817	.560	.216
.2502328	.540	.216
.2512395	.540	.209
.2673648	.520	.209
.2865111	.500	.209
.2920300	.480	.209
.3326268	.480	.203
.3724331	.480	.196
.3796284	.460	.196
.3863475	.440	.196
.3872241	.440	.190
.3877890	.420	.190
.3893991	.420	.183
.3909810	.420	.176
.3931631	.420	.170
.3957594	.420	.163
.3970783	.400	.163

.3990684	.400	.157
.4007032	.380	.157
.4011638	.380	.150
.4019196	.360	.150
.4024904	.360	.144
.4028563	.360	.137
.4032437	.360	.131
.4033733	.360	.124
.4051785	.360	.118
.4070136	.360	.111
.4094846	.340	.111
.4124733	.340	.105
.4135934	.340	.098
.4142256	.340	.092
.4148959	.320	.092
.4155767	.300	.092
.4167508	.300	.085
.4180726	.280	.085
.4190076	.280	.078
.4200692	.280	.072
.4207025	.280	.065
.4223898	.260	.065
.4264861	.240	.059
.4298031	.240	.052
.4345285	.220	.052
.4397498	.200	.052
.4437675	.200	.046
.4487552	.180	.046
.4510980	.160	.046
.4547598	.140	.046
.4640485	.140	.039
.4702348	.140	.033
.4766356	.140	.026
.4907483	.140	.020
.4990782	.120	.020
.5009972	.100	.020
.5058612	.100	.013
.5099826	.100	.007
.5175599	.100	.000
.5246319	.080	.000
.5646822	.060	.000
.6927874	.040	.000
.8277547	.020	.000
1.0000000	.000	.000

The test result variable(s): Predicted probability has at least one tie between the positive actual state group and the negative actual state group.

a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

From the above table you could see for the probability value of .1845, the sensitivity was 70% and the specificity was 58%. If we choose this as the best cut off value then we could construct the following 2 x2 table to find the validity statistics and the Positive Predictive values.

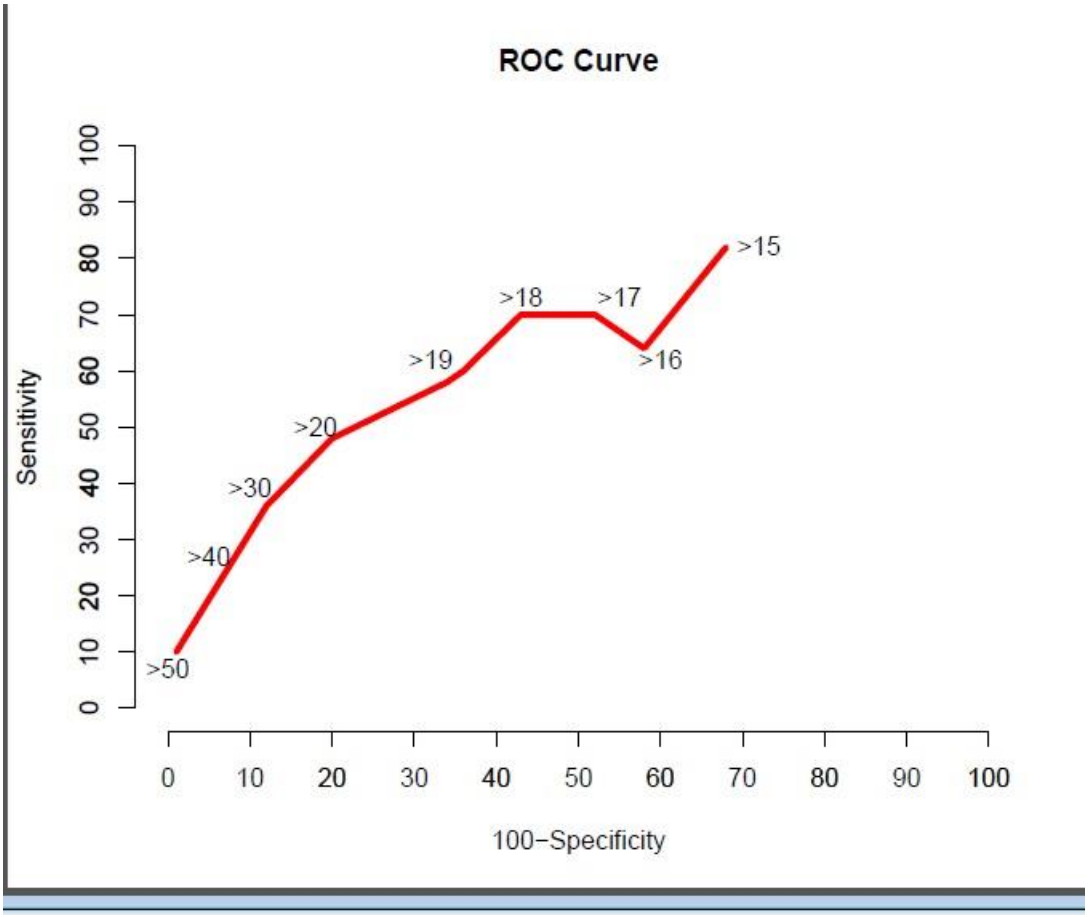
The following is nearly that table:

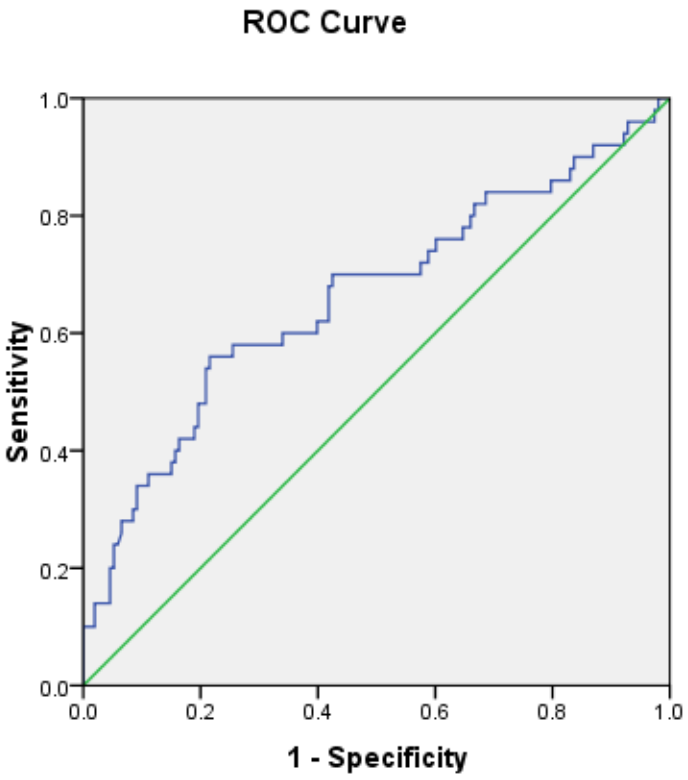
Predicted Status	**Actual Status**		
	Dead+LFU	Alive	Total
Dead+LFU	35	65	100
Alive	15	88	103
Total	50	153	203

The sensitivity is 70% and the Specificity is 58%. The positive predictive values is 35% and the negative predictive value is 85.4%.

The C statistics is .66. (this is the summary of ROC curve).

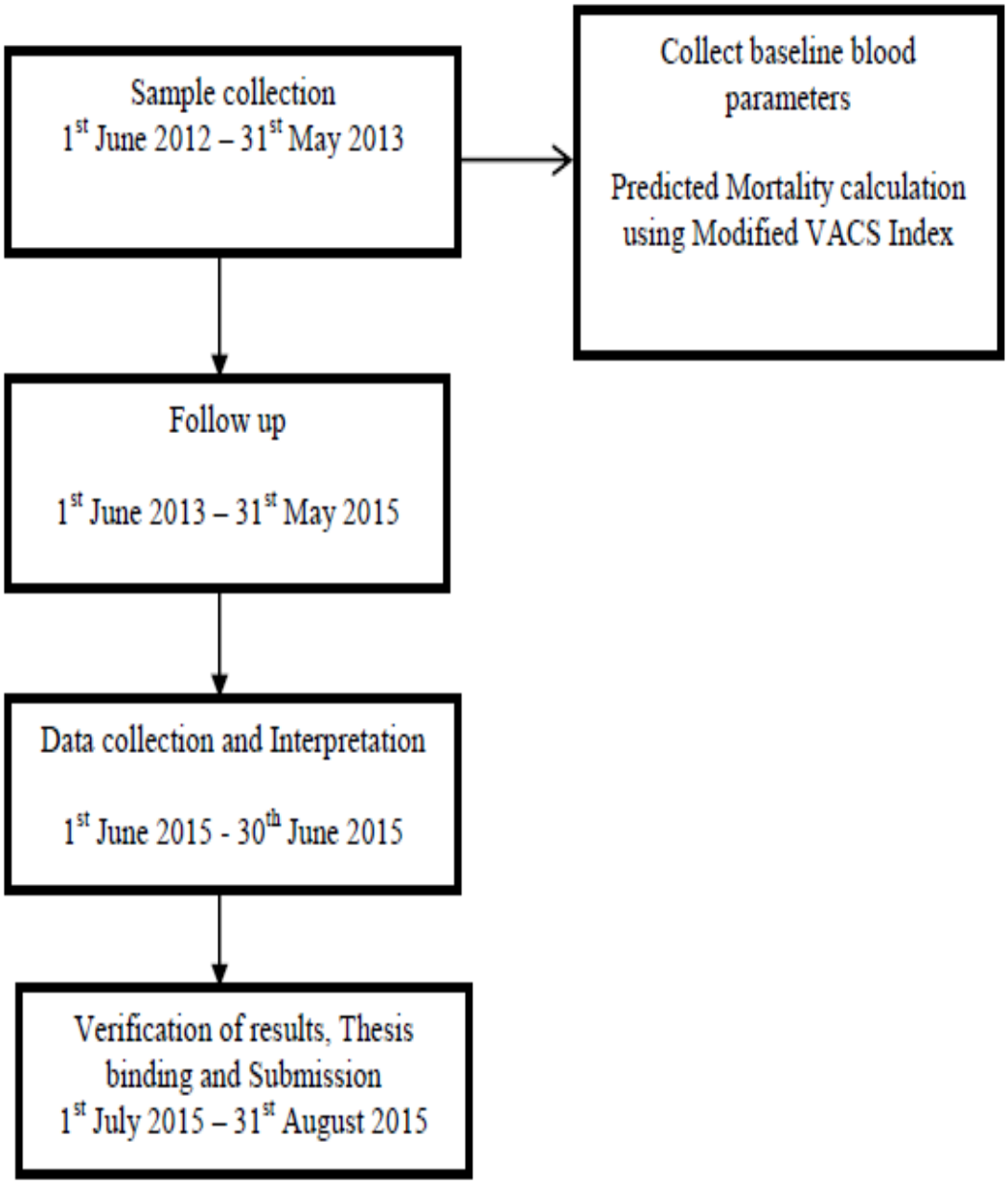
The following is the ROC Curve. I am working on a nice curve with few points.


ROC Curve
Sensitivity
0
10
20
30
40
50
60
70
80
90
100
>50
>40
>30
>20
>19
>18
>17
>16
>15
0
10
20
30
40
50
60
70
80
90
100
100−Specificity



Diagonal segments are produced by ties.

Annexure 2: PROTOCOL



APPLICATION FOR IRB APPROVAL OF OBSERVATIONAL (CASE-CONTROL / COHORT/ CROSS-SECTIONAL) STUDIES

CHRISTIAN MEDICAL COLLEGE, VELLORE

(Please complete Sections **I to III** and submit with all supporting documents)

SECTION I

Fluid Research Funding/External Funding (delete as appropriate)

If for external funding, please provide name of funding agency and the application for submission in the funding agency's format, in addition to this application.

1. **Title of Research**

   Validation of the Modified VACS Index in a South Indian Population with HIV Infection and on Initial ART Regimen under the NACO Programme : A Cohort Study

2. **Title of Study (for lay public):**

   Modified VACS Index and HIV related mortality in South India

3. **Acronym if any**

   Nil

4. **Unique Protocol ID, if any**

   Nil

5. **Name of the Principal Investigator:** Dr. Aditya John Binu

   Designation: PG Registrar

   Department : General Medicine

   Unit : I

   Employment Number: 29070

   Address for communication (including telephone and fax numbers and email id):

   Department of General Medicine , Unit – I

   Christian Medical College , Vellore

   Tamil Nadu – 632004

   Phone Number – 9940789083

   Email ID – adityabinu@gmail.com

If Post Graduate Registrar / Fellowship:

Enrollment date of PG Course: 06/2013

Completion date of PG Course: 05/2016

6. **Name of Guide (for Post-Graduate Registrar / Fellowship):** Dr. O.C. Abraham

   Employment Number: 05638

   Address for communication (including telephone and fax numbers and email id):

   Dr. O.C. Abraham

   Department of General Medicine, Unit – I

   Christian Medical College, Vellore

   Tamil Nadu – 632004

   Email ID - ocabraham@cmcvellore.ac.in

7. **Name and Designation of Co-Investigator(s), Employment Number and Address**

   Dr. Sam Prasad Mannam

   Assistant Professor

   Employment Number - 28815

   Department of General Medicine, Unit – I

   Christian Medical College, Vellore

   Tamil Nadu – 632004

8. **Department of Institution where the research will be carried out**

   Infectious Diseases Clinic

   Department of General Medicine, Unit – I

   Christian Medical College, Vellore

   Tamil Nadu – 632004

9. **Names and addresses of other institutions where research will be carried out**

   Nil

10. **Duration of the Scheme.**

From June 2012 to May 2015

11. Source/s of Monetary or Material Support

Internal Fluid Research Grant : Yes

External : No

Departmental fund : If needed

12. Objectives and aims of study (*including any hypotheses).*

Aims:

To validate the Modified VACS Index in a South Indian Population infected with HIV.

Objectives:

i. To predict patient mortality in HIV infected patients attending the ID clinic who have been started on ART regimen under NACO over a 1 year period from 1st June 2012 to 31st May 2013 and follow up over a 2 year period from 1st June 2013 to 31st May 2015 using the Modified VACS index using baseline blood parameters.

ii. To compare predicted mortality with actual mortality in the cohort over a 2 year period from 1st June 2013 to 31st May 2015.

iii. To use this data to design and implement effective interventions to improve outcomes among patients with HIV infection

13. Summary of the proposed research scheme (250 words).

The Veterans Aging Cohort Study (VACS) Risk Index , is a composite index which was designed to predict mortality in HIV patients who have been treated for one year with ART, using a simple scoring system. The VACS Index was developed in HIV-infected US veterans and validated in independent cohorts from the US and Europe participating in the Antiretroviral Therapy Cohort Collaboration (ART-CC). It comprises of basic blood parameters measured routinely in HIV clinics viz. Age, CD 4 count , Hemoglobin, HIV-RNA viral load, AST, ALT, Platelet count, Serum Creatinine and Hepatitis C infection.

In our study, we attempt to validate a modified VACS Index (avoid HIV RNA PCR) in a South Indian population with HIV infection by comparing the predicted mortality, which is gauged at baseline using the index, with actual mortality over a duration of 2 years from 1st June to 31st May 2015. The sample is to be taken from a South Indian population with HIV infection and started on 1st line Anti-retroviral therapy (ART) under the NACO scheme during the period from 1st June 2012 to 31st May 2013. The primary outcome under study

is mortality due to any cause. We also attempt to correlate mortality with individual blood parameters. The Modified VACS Index could be used as a prognostic tool and assess chances of favourable outcomes in patients attending an HIV clinic.

14. Present Knowledge and relevant bibliography *(Is there a justification for this study based on a detailed literature review or other sources of evidence? Please provide details)*

The global pandemic of HIV has seen some momentary relief subsequent to the introduction of ART.(1) As per national statistics for 2012 , India has demonstrated an overall reduction of 57% in the annual new HIV infections (among adult population) from 2.74 lakhs in 2000 to 1.16 lakhs in 2011, as a consequence of various interventions and prevention strategies under the National AIDS Control Programme (NACP).(2) The adult HIV prevalence has also shown a significant decrease from 0.41% in 2001 to 0.27% in 2011.(2) The estimated number of people living with HIV has decreased from 24.1 lakh in 2000 to 20.9 lakhs in 2011.(2)Greater access to ART has resulted in 29% decrease in estimated annual deaths due to AIDS related causes (ARC) between 2007 and 2011.(2)An estimated 1.5 lakhs lives have been saved due to ART till 2011.(2)

Yet compared to behaviourally and demographically similar controls, excess mortality in these individuals remains and is not explained by CD4 count alone .(3) Studies suggest that HIV-associated inflammation , hypercoagulability , and increased risk of aging-associated organ system injury may contribute to this excess.(4)

The Veterans Aging Cohort Study (VACS) Risk Index, is a composite index to predict mortality in HIV patients who have been treated for a year, using a simple scoring system.(5) The VACS Index was developed in HIV-infected US veterans and validated in independent cohorts from the US and Europe participating in the Antiretroviral Therapy Cohort Collaboration (ART-CC).(5) It comprises of nine baseline blood parameters measured routinely in patients with HIV infection viz. Age, CD 4 count, Haemoglobin, HIV-1 RNA viral load, AST, ALT, Platelet count, Serum Creatinine and Hepatitis C infection.(5)

The VACS Index was compared with a Restricted Index comprising 3 parameters only – Age, CD 4 counts and HIV-1 RNA.(5,6) The VACS Index was found to have a better discrimination than the Restricted Index in both validation and development cohorts.(5) It was also found to have better discrimination for HIV and non-HIV deaths, men and women, below and above 50 years, with and without detectable HIV-1 RNA and with or without HCV coinfection.(5)

References:

1. Kazanjian P. The AIDS Pandemic in Historic Perspective. J Hist Med Allied Sci. 2012 Oct 22;
2. Department of AIDS Control , Ministry of Health & Family Welfare, Annual Report 2012-13.
3. Justice AC. HIV and aging: time for a new paradigm. Curr HIV/AIDS Rep. 2010 May;7(2):69–76.
4. Kuller LH, Tracy R, Belloso W, Wit SD, Drummond F, Lane HC, et al. Inflammatory and Coagulation Biomarkers and Mortality in Patients with HIV Infection. PLoS Med [Internet]. 2008 Oct [cited 2013 Oct 16];5(10). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2570418/
5. Tate JP, Justice AC, Hughes MD, Bonnet F, Reiss P, Mocroft A, et al. An internationally generalizable risk index for mortality after one year of antiretroviral therapy. AIDS Lond Engl. 2013 Feb 20;27(4):563–72.
6. Justice AC, McGinnis KA, Skanderson M, Chang CC, Gibert CL, Goetz MB, et al. Towards a combined prognostic index for survival in HIV infection: the role of "non-HIV" biomarkers. HIV Med. 2010 Feb;11(2):143–51.

15. Preliminary work already done by the investigator in this problem

- Nil

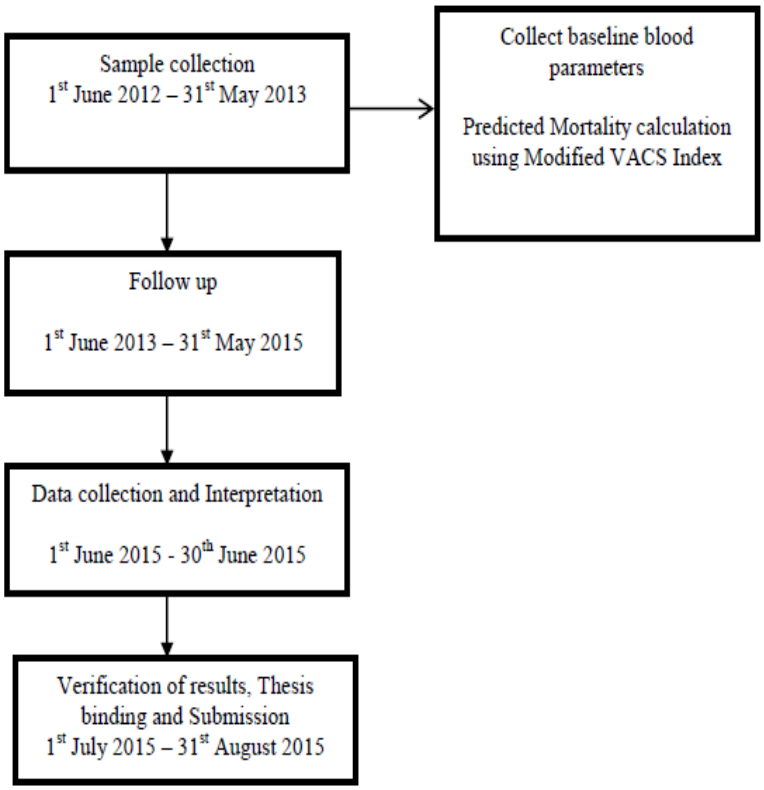
16. List of publications of the investigator in the field

- Nil

17. Structured abstract

- The Modified VACS Index is intended to be used as a prognostic aid in PLHIV who have been initiated on 1st line anti-retroviral therapy to predict mortality, assess modifiable co-morbidities and assess efficacy of treatment. The index is derived from blood investigations which are routinely performed on PLHIV in the Infectious diseases (ID) clinic. The VACS index has already been validated in European and North American populations. We are attempting to validate a modified form of the same index, in a South Indian population. The cohort will be chosen retrospectively from the period 1st June 2012 – 31st May 2013 from PLHIV started on 1st line NACO ART and will be followed up for a period of 2 years. Mortality is the primary outcome of interest. We will compare the predicted mortality using the Modified VACS Index, with the observed mortality after 2 years using a Standard Mortality ratio (SMR).

18. Detailed diagrammatic Algorithm of the study



19. Detailed research plan:

a. **Setting:** Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection

   a. Setting and location:

Infectious Diseases Clinic

Department of General Medicine, Unit – I

Christian Medical College, Vellore

Tamil Nadu – 632004

b. Data collection: Data will be collected from the patient's medical records.

c. Relevant dates:

	Planned Dates	Actual Dates
Recruitment	June 2012 – May 2013	
Research Question	August 2013	September 2013
Protocol Development	August 2013	September 2013
IRB Submission	September 2013	October 2013
Account Dept. Submission	October 2013	
Data Entry Start	November 2013	
Thesis Submission to Guide	August 2015	
Formatting of Thesis	August 2015	
Submission of Thesis	August 2015	

Follow up: June 2013 – May 2015

b. **Participants:** Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases (and controls, if applicable). For matched studies, give matching criteria and the number of controls per case

a. Inclusion Criteria:

- PLHIV started on first line NACO ART regimen from ID clinic in CMC Vellore during the period from 1st June 2012 to 31st May 2013.

b. Exclusion Criteria:

- PLHIV started on ART before or after the specified period (1st June 2012 – 31st May 2013).
- PLHIV started on non-NACO ART .

c. **Variables:** Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

i. Age

- < 50 years
- 50 – 64 years

- > / = 65 years

ii. Gender
- Male
- Female

iii. CD4 count
- > 500 / mm^3
- 350 – 499 / mm^3
- 200 – 349 / mm^3
- 100 – 199 / mm^3
- 50 – 99 / mm^3
- < 50 / mm^3

iv. Haemoglobin
- > 14 g / dl
- 12 – 13.9 g / dl
- 10 – 11.9 g / dl
- < 10 g / dl

v. AST
vi. ALT
vii. Platelets
} FIB-4

viii. Creatinine ⟶ eGFR

ix. Hepatitis C infection

d. **Data Sources/measurement:** For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group

Variable	Source of data	Method of assessment
1.Age	Medical record	
2.Gender	Medical record	
3. CD4 count	Blood report	
4. Haemoglobin	Blood report	
5. AST	Blood report	
6. ALT	Blood report	
7. Platelets	Blood report	
8. Creatinine	Blood report	
9. Hepatitis C co-infection	Blood report	

e. **Bias:** Describe any efforts to address potential sources of bias

- Standardized protocols to be followed as per NACO guidelines.

f. Sample size:(It may be suitable to have a statistician as a co-investigator)

Explain how the study size was calculated

Explain how the study size was calculated

- $n = \frac{Z * p * q}{d^2}$

Z = Standardized normal deviate
p = proportion / prevalence of mortality in population of interest
q = 100 – p
d = Clinically expected variation

For the year 2012 – 2013 , the total population of PLHIV started on first line NACO – ART was 353 with an outcome of mortality in 31.

Prevalence of mortality (p) = 31/353 = 8.8 %

Anticipating a clinical variation (d) of 3.5% , and a Z – value for a 95 % confidence interval corresponding to 1.96,

- $n = \frac{(1.96)^2 \times 8.8 \times 91.2}{(3.5)^2} = 252$

g. **Quantitative variables:** Explain how quantitative variables will be handled in the analyses. If applicable, describe which groupings were chosen and why

i. CD4 count
ii. Haemoglobin
iii. AST
iv. ALT
v. Platelets
vi. Creatinine
vii. Age

h. **Statistical methods:** Describe all statistical methods, including those used to control for confounding and examine subgroups and interactions. How will missing data be

handled? If applicable, how will matching of cases and controls be handled? Describe any proposed sensitivity analyses.

- The observed mortality will be compared with the expected mortality by using a standardized mortality ratio. The expected mortality will be derived from the VACS index using Cox hazard ratios.
- Analysis will be done under guidance of statistician.
- Missing data will be mentioned and analysis will be done based on available data.

20. Complete budget plan

*For **FLUID research grant money cannot be allocated for travel of the investigators nor can job outsourcing** be covered with FLUID grants. Funding out of the institution can be given only for the special mission hospital grant*

*(From Fluid Research Fund, there are no grants for personnel except in a major grant application, funding is limited **Rs. 50,000/- per year** for two years for standard applications, **Rs. 2,00,000/- per year for two years for major applications**). Website link: http://172.16.11.136/Research/#. > Rules for Major Fluid Research Grants. Do not exceed the budget allocated to you. In case the budget is exceeded, the amount will have to be deducted from one of your departmental special funds. Stationary, printing material and paper should not exceed more than 20% of the allocated fluid grant.*

*Please mention below the **breakdown of budget requested:** (The budgets that are drawn up should be comprehensive and should mention all subject in detail (For example – laboratory investigation should mention the specific category without generalization.)*

S. No.	Item	Cost (Rs.)/unit	Total No.	Total cost (Rs.)
1	Printing/copying	2	2500	5000.00
2	Binding	50	6	300.00
3	Miscellaneous	---	---	1000.00
Total	Estimated cost in total	---	---	6300.00

21. If this is an application for Fluid Research Funding, please provide name and account number of any other Fluid Research grant held by the PI.

- None

22. **Informed Consent Documents (patient information sheet, investigator's brochure, drug information etc and informed consent document)** please submit all translations with the proposal.

- Enclosed with application form.

23. **Publication Plans:** (List all potential authors and their likely contributions)

(Please tick √ appropriate box)

	Responsibilities			
Author(s) name	Research and Study design	Data collection & analysis	Laboratory analysis	Interpretation and conclusion
Dr. Aditya John Binu	yes	yes		yes
Dr. O. C. Abraham				
Dr. Sam P. Mannam				

	Responsibilities				
Author(s) name	Preparation of Manuscript	Review of Manuscript	Guide and Critical revision	Administration	Technical Support
Dr. Aditya John Binu	yes	yes			
Dr. O. C. Abraham		yes	yes		
Dr. Sam P. Mannam		yes	yes		

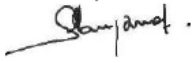
24. **Inter-departmental cooperation:** (Please describe the arrangements with institutional diagnostic service units/departments that are being used for this research project, if applicable).

25. **Signature of Principal Investigator** 

26. Signature of Guide/Head of the Department/ Unit

27. Co-Investigators' Consent (all co-investigators have to sign this form or supply separate letters of consent)

I/We give my/our consent to be a Co-Investigator and provide my/our expertise to the project. I/We have approved this version of the protocol and have contributed substantially to its development.

Name	Department	Signature	Date
Dr. O. C. Abraham	General Medicine – I		14–11–2013
Sam P. Mannam	General Medicine - I		14–11-2013

Section II

APPLICATION FOR APPROVAL FROM ETHICS COMMITTEE OF THE INSTITUTIONAL REVIEW BOARD OF CMC VELLORE FOR ALL OBSERVATIONAL (CASE CONTROL, COHORT & OBSERVATIONAL) STUDIES IN HUMAN SUBJECTS

1. **Please provide a brief summary of the justification, objectives and methods in lay language, avoiding technical terms.**

    - The Modified VACS Index is intended to be a tool to assess the chances of improvement of patients with HIV infection who have been started on anti-retroviral drugs from the Infectious diseases (ID) clinic. This study uses blood investigations which are routinely performed on patients attending the HIV clinic. It is also to be used as a tool to predict patient mortality from routine blood investigations, in addition to assessing pre-treatment status of the patient. The VACS index has already been validated in European and North American populations. We are attempting to validate a modified form of the same index in a South Indian population.

2. **Please describe if the study uses procedures already being performed on patients for diagnosis or treatment or if modified or novel procedures are to be used?**

    - This study uses blood investigations which are routinely performed on every patient attending the HIV clinic. No other investigation will be utilised in this study.

3. **Please describe what benefits might be reasonably be expected by the participant as an outcome of participation**

    - The chief benefit to be derived from this study will be to obtain an index to assess the prognosis of a patient prior to starting treatment at no additional cost.

4. **Please describe what benefits to others or new knowledge might be expected as a result of this study**

    - The modified VACS Index will aid doctors in assessing patient prognosis at the time of initiation of anti-retroviral therapy.
    - It will help in the modification of other risk factors which may influence patient prognosis. Eg. Alcoholism, Hepatitis C
    - Efficacy of treatment may be assessed .

5. **Who are to be enrolled?**

- HIV infected patients of any age attending the ID clinic who are to be started on first line ART as per existing NACO protocols.

6. **If any vulnerable groups (e.g., pregnant women, children) are to be enrolled, please provide a justification for their inclusion.**

   - No

7. **If any economically disadvantaged individuals are to be enrolled, please provide a justification for their inclusion.**

   - No

8. **What are the potential risks to participants in this study?**

   - Nil

9. **Are the risks to participants reasonable in relation to the benefits that might reasonably be expected as an outcome to the participant or to others, or the importance of the knowledge that may reasonably be expected to result? Please provide a detailed description of the above.**

   - Not applicable

10. **Regarding informed consent to obtained from research participants or their legally authorized representative(s):**

    a. **Does the informed consent document include all the required elements?**

       - Yes

    b. **Are the participant information sheet and the consent document in language understandable to participants? (PLEASE PROVIDE WITH THIS SUBMISSION TRANSLATIONS IN ALL LOCAL LANGUAGES ANTICIPATED TO BE USED).**

       - Yes

    c. **Who will obtain informed consent (PI, nurse, other?) and in what setting?**

       - Principal investigator

- HIV counselor

d. **If appropriate, is there a children's assent? If yes, please submit a copy of this form.**

- No

e. **Is the EC requested to waive or alter any informed consent requirement?**

- No

11. Is there provision of free treatment for research related injury? If yes, who will provide it?

- No

12. Is there provision for compensation of participants for disability or death resulting from research related injury. If yes, who will provide it?

- No

13. Is the study covered by insurance? If yes, please provide insurance documents from an Indian insurance company.

- No

14. In addition to the overall budget in Section I, please provide details of the following

i) Justification, timing and amount of payments to study participants

- Not applicable

ii) Justification, timing and amount of payments to investigators/departments

- Not applicable

iii) Any other study related financial or in kind incentives to participants or study staff

- Not applicable

15. Please describe the plan for maintaining confidentiality of study participant information.

- All patient details will be kept confidential and only the data collected from his / her records will be used for analysis.

16. **Please describe the plans for monitoring the safety of participants, reporting and managing adverse events. If this is an externally funded study with a Data Safety Monitoring Board, please provide the name and contact information of the DSMB chairperson.**

    - Not applicable

17. **If applicable; please provide all significant previous decisions (e.g., those leading to a negative decision or modified protocol) by other ECs or regulatory authorities for the proposed study (whether in the same location or elsewhere) and an indication of the modification(s) to the protocol.**

    - Not applicable

18. **If appropriate, has permission from the Drug Controller General of India been obtained?**

    - Not applicable

19. **If this is international collaborative research, has permission from the Health Ministry's Screening Committee been obtained?**

    - Not applicable

20. **For exchange of biological material in international collaborative studies, please provide a Memorandum of Understanding (MOU)/ Material Transfer Agreement (MTA) between the collaborating partners.**

    - Not applicable

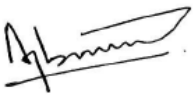
21. **Declaration (to be signed by all investigators)**

By signing this form we give our consent to provide our expertise to the project. In addition:

a. We confirm that all investigators have approved this version of the protocol and have contributed substantially to its development.
b. We confirm that all potential authors are included in this protocol.
c. We confirm that we shall submit any protocol amendments, significant deviations from protocols, progress reports (if required) and a final report and also participate in any audit of this study, if required.
d. We confirm that we shall conduct this study in accordance with the Declaration of Helsinki; the ICMR Guidelines for Biomedical Research in Human Subjects 2006, with any subsequent amendments; and all applicable laws of the land.
e. We also agree to submit for publication to a peer reviewed journal the complete results of this study within two years of completion of this study.

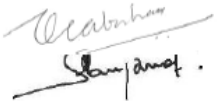
f. We declare that we have no conflicts of interest that may affect the conduct or reporting of this study (OR) we declare the following conflicts of interest below.
g. We are aware of the institution's policies regarding scientific misconduct (Falsification/fabrication/plagiarism) and agree to abide by them.

22. Signature of Principal Investigator



23. Signature of Guide/Head of the Department/ Unit

24. Co-Investigator's Consent (all co-investigators have to sign this form or supply separate letters of consent)

Name	Department	Signature	Date
Dr. O.C. Abraham	General Medicine		14-11-2013
Dr. Sam Prasad Mannam	General Medicine		14-11-2013

Conflicts of interest if any:

- None

Annexure 3: CLINICAL RESEARCH FORM

CLINICAL RESEARCH FORM

(Modified VACS Index and HIV Related Mortality In South India)

SUBJECT ID NUMBER

HOSPITAL NUMBER

NAME

AGE : GENDER : **MALE/ FEMALE**

years

ADDRESS:

CD4 COUNT : HAEMOGLOBIN :

AST : ALT :

PLATELETS :

CREATININE : HEPATITIS - C : **POSITIVE / NEGATIVE**

OUTCOME :

Annexure 4: CONSENT FORMS

English

Informed Consent form to participate in a research study

Study Title: Modified VACS Index and HIV related mortality in South India

Study Number: _____

Subject's Initials: _____ **Subject's Name:** _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

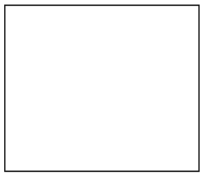
(v) I agree to take part in the above study.

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: ____/____/_____

Signatory's Name: _____ Signature:

Or



Representative: _____

Hindi

सूचित सहमति फार्म

अध्ययन शीर्षक : एचआईवी संक्रमण के साथ एक दक्षिण भारतीय जनसंख्या में और प्रारंभिक मुफ्त एआरटी परहेज पर संशोधित Vacs सूचकांक की मान्यता: एक पलटन अध्ययन

अध्ययन क्रमांक :

रोगी का नाम : _____

उम्र/जन्म तिथि : _____

(i) मैं पुष्टि करता/करती हूँ कि मैंने उपर लिखे अध्ययन के बारे में जानकारी पत्र दिनांकित 25-10-2013 को पढ़ व समझ लिया है और मुझे सवाल पूछने का अवासर मिला है।

(ii) मैं समझता/समझती हूँ कि इस अध्ययन मे भाग लेना स्वैच्छिक है और यह कि मैं किसी भि वक्त नाम वापस ले सकता/सकती हूँ, बिना कोई कारण बताए, बिना मेरी चिकित्सा देखभाल व कानूनी अधिकार प्रभावित हुए।

(iii) मैं समझता/समझती हूँ कि चिकित्सीय परीक्षण के प्रायोजक, प्रायोजक कि ओर से काम कर रहे अन्य लोग, नैतिक समिति और नियामक अधिकारीयों को मेरी अनुमति कि जरुरत नहीं होगी मेरा स्वास्थ रिकार्ड को देखने के लिए इस अध्ययन या आगे इससे संबंधित अगर कोई रिसर्च होता है, अगर मैं अपना नाम वापस ले लेता हूँ तौ पर भी। मैं इसके उपयोग के लिए सहमत हुँ। और मैं समझता/समझती हूँ कि मेरी पहचान किसी तीसरे पक्ष को जारी या प्रकाशित नहीं किया जाएगा।

(iv) मैं बाधा उत्पन नहीं करने के लिए सहमत हूँ इस अध्ययन के कोई भी डाटा या परिणाम के उपयोग का बशर्ते उपयोग सिर्फ वैज्ञानिक उद्देश्य से हो।

(v) मैं इस अध्ययन मे भाग लेने के लिए सहमत हूँ।

रोगी/कानूनी तौर पर स्वीकार्य का हस्ताक्षर

दिनांक: ____/____/_____

हस्ताक्षरकर्ता का नाम: _____ हस्ताक्षर:

या

Tamil

ஆராய்ச்சியில் பங்குபெறுவதற்கான ஒப்புதல் படிவம்

ஆராய்ச்சியின் தலைப்பு:

மாற்றியமைக்கப்பட்ட VACS வழிகாட்டி மற்றும் தென் இந்தியாவின் எச்.ஐ.வி. சார்ந்த இறப்புக் கணக்கு.

ஆராய்ச்சியின் எண்:

பங்கு கொள்பவரின் முதல் _____ எழுத்து பெயர் _____

பிறந்த தேதி _____ வயது _____

1. எனக்கு இந்த ஆராய்ச்சி குறித்து முழுத் தகவல்களும் கூறப்பட்டு முழுமையாக புரிந்க் கொண்டேன்.
2. கேள்விகள் கேட்க வாய்ப்பு அளிக்கப்பட்டது.
3. இந்த ஆராய்ச்சியில் நான் பங்கு கொள்வது தன்னார்வத்தை சார்ந்தது என்றும் எப்போது வேண்டுமானாலும் விலகிக் கொள்ளலாம் என்பதையும் அறிந்துக் கொண்டேன். அவ்வாறு விலகுவதால் என்னுடைய சிகிச்சையும் மற்றும் என்னுடைய உரிமையும் எந்த விதத்திலும் பாதிக்காது என்பதை அறிந்து கொண்டேன்.
4. இந்த ஆராய்ச்சிக்காக பணம் கொடுப்பவர்கள் மற்றும் நடத்துபவர், நெறிமுழு மற்றும் கட்டுப்பாட்டு அதிகாரிகள் ஆகியோர் என்னுடைய மருத்துவ பதிவேடுகளை பார்க்கவும். இந்த ஆராய்ச்சியின் முடிவுகளை எதிர்கொண்டிருக்கும் ஆராய்ச்சிக்கு பயன்படுத்தவும் என்னுடைய அனுமதி தேவையில்லை என்பதையும் அறிந்துக்கொண்டேன் ஒருவேளை நான் ஆராய்ச்சியில் இருந்து விலகிக் கொண்டாலும் ஆனாலும் என்னுடைய அடையாளம் யாராலும் கண்டறியாதபடி கையாளப்படும் என்பதை அறிந்துக் கொண்டேன்.

5. அறிவியல் பூர்வமாக என்னுடைய தகவல்களை பயன்படுத்தவும் மற்றும் ஆராய்ச்சியின் முடிவுகளை பயன்படுத்தவும் என்னால் தடை செய்ய முடியாது என்பதையும் அறிந்துக் கொண்டேன்.
6. இந்த ஆராய்ச்சியில் பங்கு கொள்ளவதற்க்கு ஒப்புதல் அளிக்கிறேன்.

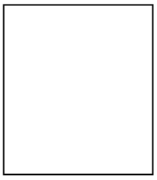
கையொப்பம் (அல்லது) பெருவிரல் முத்திரை/சட்டபூர்வமாக அனுமதிக்கப்பட்டவர்கள்.

பெயர் : _____

தேதி : _____

(or)

பெருவிரல் முத்திரை:



பிரதிநிதி : _____

தேதி : _____

கையெழுத்திடுபவரின் பெயர் : _____

ஆராய்ச்சியாளரின் கையொப்பம் : _____

சாட்சியின் கையொப்பம் மற்றும் விலாசம் : _____

தேதி : _____

Annexure 5: Information Sheets

English

Postgraduate Research Study

Validation of the Modified VACS Index in a South Indian Population with HIV Infection and on Initial ART Regimen under the NACO Programme : A Cohort Study

INFORMATION SHEET FOR PARTICIPANTS

You are being invited to be involved in this research study. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with other members of your family if you wish. Please contact me if anything is unclear or if you would like more information. Take time to decide whether or not you wish to take part.
Thank you for reading this.

What is the purpose of the study?

- This study is being done to derive an index or a simple mathematical tool (using blood investigations which are routinely performed on patients attending the HIV clinic) which is intended to be used as a tool to assess pre- treatment status of the patient, chances of improvement in the patient's condition, other risk factors like alcoholism etc. which can be potentially modified, and most importantly efficacy of the treatment you receive. In simple words, it can be used to find out whether there is a good chance of patient survival with the best possible treatment.

Why have I been chosen?

- You are being invited to take part in this study because you have been started on first line Anti-Retroviral Therapy (ART) from our Infectious Diseases Clinic as per the National AIDS Control Organisation (NACO) Guidelines and are about to complete or have already completed one year of treatment.

What will participation involve?

- Participation involves giving consent for us to use the blood investigations which you had given as part of your routine assessment just prior to (up to 6 months) starting your ART. The data will be recorded in data sheets, and later transcribed into tabular form. This data will be anonymised, so that you cannot be identified. You would be very welcome to a copy of the final report if you wish.

Please note that:

- You can decide to withdraw from the study anytime until 31st May 2015.
- Your name will be removed from the information and anonymised. It should not be possible to identify anyone from my reports on this study.

It is up to you to decide whether to take part or not. If you withdraw from the study, all data concerning you will be withdrawn and destroyed.
If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form.

Contact for further information

Department of General Medicine – I
Christian Medical College,
Vellore – 632004
Tamil Nadu

Thank you

Hindi

स्नातकोत्तर अनुसंधान अध्ययन

एचआईवी संक्रमण के साथ एक दक्षिण भारतीय जनसंख्या में और प्रारंभिक मुफ्त एआरटी परहेज पर संशोधित VACS सूचकांक की मान्यता: एक पलटन अध्ययन

प्रतिभागियों के लिए जानकारी शीट

इस शोध अध्ययन में शामिल होने के लिए आप को आमंत्रित किया जा रहा है . यदि आप भाग लेना चाहते हैं, उस से पहले यह शोध क्यों किया जा रहा है, यह कारण समझना महत्वपूर्ण है . निम्नलिखित जानकारी ध्यान से पढ़ें और यदि आप चाहें तो अपने परिवार के अन्य सदस्यों के साथ इस पर चर्चा करने के लिए समय ले. यदि आप अधिक जानकारी चाहते हैं, या कुछ स्पष्टीकरण चाहते हैं तो मुझे संपर्क करें.यह जानकारी पढ़ने के लिए धन्यवाद .

इस अध्ययन का उद्देश्य क्या है ?

• इस अध्ययन से हम एक सूचकांक का निर्माण करना चाहते हैं जो मरीज के इलाज से पहले की स्थिति का आकलन करने के लिए एक उपकरण के रूप में इस्तेमाल हो. यह सूचकांक एचआईवी क्लिनिक के रोगियों के रक्त जांच से प्राप्त किया जाएगा. इस सूचकांक से मरीज की हालत में सुधार की संभावना , शराब आदि जैसे अन्य जोखिम वाले कारकों का प्रभाव और प्राप्त उपचार का प्रभावकारिता नापा जा सकता है . सरल शब्दों में, इस सूचकांक से सबसे उपयुक्त उपचार के साथ रोगी के जीवित रहने का एक अच्छा पूर्व अनुमान लगाया जा सकता है .

मैं क्यों चुना गया हूँ ?

आप को राष्ट्रीय एड्स नियंत्रण संगठन (नाको) के दिशा निर्देशों के अनुसार हमारे संक्रामक रोग क्लिनिक से पहली पंक्ति एंटी रेट्रोवायरल थेरेपी (एआरटी) पर शुरू किया गया है .

• आप को इस अध्ययन में भाग लेने के लिए इस लिए आमंत्रित किया जा रहा है क्योंकि आप ने इलाज का एक वर्ष पूरा किया है या करने वाले हैं.

भागीदारी में क्या शामिल होगा ?

• भागीदारों को हमें अपने एआरटी की शुरुआत से पहले (6 महीने तक) किये गए रक्त जांच के आंकड़ों का उपयोग करने के लिए सहमति देना होगा. इस जानकारी को डेटा शीट में दर्ज किया जाएगा, और बाद में सारणीबद्ध रूप में लिखा जाएगा . आप से संबंधित जानकारी को गोपनीय रखा जाएगा . अंतिम रिपोर्ट की एक प्रति के लिए आप कभी भी अनुरोध कर सकते हैं.

कृपया ध्यान दें कि :

♣ आप 31 मई 2015 तक कभी भी अध्ययन से नाम वापस लेने का फैसला कर सकते हैं .
♣ अगर आप अध्ययन से नाम वापस ले, आप से संबंधित जानकारी को हटा दिया जाएगा और गोपनीय रखा जाएगा. इस अध्ययन के रिपोर्टों से किसी को पहचानना संभव नहीं होना चाहिए .

भागीदारी का फैसला आप पर निर्भर है . अगर आप अध्ययन से नाम वापस ले, तो आप से संबंधित सभी डेटा को नष्ट कर दिया जाएगा .अगर आप भाग लेने का फैसला करते हैं, तो आप को यह सूचना पत्रक रखने के लिए दिया जाएगा और हस्ताक्षर करने के लिए एक सहमति पत्र दिया जाएगा .

अधिक जानकारी के लिए संपर्क करें

जनरल मेडिसिन विभाग - 1
क्रिश्चियन मेडिकल कॉलेज ,
वेल्लोर - 632004
तमिल नाडु

धन्यवाद.

Tamil

பங்கேற்பவர்கான தகவல் படிவம்

மாற்றியமைக்கப்பட்ட VACS வழிகாட்டி மற்றும் தென் இந்தியாவின் எச்.ஐ.வி. சார்ந்த இறப்புக் கணக்கு

எச்.ஐ.வி.பரிசோதனை படிப்பதற்கான ஆய்வில் பங்கேற்ப்பதற்காக நன்றி. இந்த ஆய்வில் கலந்துக்கொள்வதற்க்கு முன்னதாக ஒவ்வொருவரின் பங்கு என்ன என்பதையும், இந்த ஆய்வு எதற்க்காக செய்யப்படுகிறது என்பதையும் மேலும் ஆய்வை பற்றிய தகவல்களை அனைவரும் அறிந்திருக்க வேண்டும். மேலும் கீழ்கண்ட தகவல்களை தெளிவாகவும், (கவனமாகவும்) பொறுமையாகவும் படித்து அதைப்பற்றி செய்திகளை தெரிந்த நண்பர்களுடனும் மேலும் தனது குடும்பத்தினரிடையேயும் கலந்து ஆலோசிக்கலாம். இந்த ஆய்வைப் பற்றிய குழப்பங்கள், சந்தேகங்கள் மேலும் விவரங்கள் தெரிந்து கொள்ள எங்களை அணுகலாம்.

ஆராய்ச்சி எதற்காக:

இந்த ஆராய்ச்சியின் மூலம் எச்.ஐ.வி ஆல் பாதிக்கப்பட்டவர்களின் சிகிச்சைக்கு முன் இருக்கின்ற நிலைமையை அறியவும். நோயாளியின் உடல்நிலை முன்னேற்றத்திற்கான வாய்ப்பை கண்டறியவும் மற்றும் மற்ற நோய்கள் அதற்கான காரணங்களை கண்டறிய மற்றும் குடிபழக்கத்தினால் ஏற்படும் பாதிப்புகளை எச்.ஐ.வி.ஆல் பாதிக்கப்பட்டவர்களிடம் செய்யும் வழக்கமான இரத்தப் பரிசோதனையின் மூலம் கண்டறிய ஒரு வழிகாட்டியை (அ) கணக்கை கொண்டுவர மற்றும் வழங்கப்படுகின்ற சிகிச்சை உங்களுக்கு முழுமையாக பயன் அளிக்கின்றதா என்பதையும் தெரிந்து கொள்ள உதவுகிறது. சுலபமாக புரிந்து கொள்ள வேண்டும் என்றால் நோயாளியின் ஆயுட்காலம் நல்ல வாய்ப்பை வழங்கப்படுகின்ற சிகிச்சை மூலம் பெற்றுள்ளதா என்பதை கண்டறியப்படுகிறது.

நான் ஏன் தேர்ந்தெடுக்கப்பட்டுள்ளேன்:

நீங்கள் முதல்கட்ட ஏ.ஆர்.டி மாத்திரையை ஆரம்பித்து ஏறக்குறைய ஓராண்டு காலம் ஆகும் தருவாயில் இருப்பதால் இந்த ஆராய்ச்சிக்காக தேர்ந்தெடுக்கப்பட்டுள்ளீர்கள்.

ஆராய்ச்சியின் உங்களின் பங்கு என்ன:

இந்த ஆராய்ச்சியில் பங்கேற்ப்பதற்கு ஒப்புதல் அளிப்பதன் மூலம் நீங்கள் ஏற்கனவே ஆறு மாதங்கள் முன்பு வரை கொடுக்கப்பட்டுள்ள இரத்தப் பரிசோதனையின் முடிவுகளை ஆராய்ச்சிக்காக பயன்படுத்துகின்றோம். இந்த ஆராய்ச்சிக்காக பயன்படுத்தப்படும் மருத்துவத் தகவல்களை யாராலும் அடையாளம் கண்டுக்கொள்ள இயலாது. மேலும் இந்த ஆராய்ச்சியின் முடிவுகளின் அறிக்கையை விரும்பினால் தேவைப்படுவோர் பெற்றுக்கொள்ளலாம்.

உங்கள் கனிவான கவனத்திற்க்கு:

1. இந்த ஆராய்ச்சியிலிருந்து நீங்கள் எப்போது வேண்டுமானலும் விலகிக் கொள்ளலாம்.
2. உங்களை அடையாளம் கண்டுகொள்ளாத படி இரகசிய எண் பயன்படுத்தப்படும்.
3. இந்த ஆராய்ச்சியில் இருந்து நீங்கள் விலகும்போது உங்களைப் பற்றிய அனைத்து தகவல்களையும் அழிக்கப்படும்.

மேலும் விவரங்களுக்கு:

Annexure 6: DATA SHEET

Sex	CD4 ct.	Hb	AST	ALT	Platelets	FIB-4	Creat(mg/c	Creat(mmc	eGFR	HCV	MVI	5 yr Mortal	Outcome
Female	42	9.9	93	52	196	2.43	0.98	86.632	68	Negative	73	50	Death
Female	160	9.8	26	14	218	1.21	1.03	91.052	64	Negative	48	25.5	Alive
Male	231	7.7	14	20	142	1.12	19.8	1750.32	3	Negative	82	58.4	LFU
Female	170	3.1	23	16	270	0.55	0.74	65.416	101	Negative	48	25.5	Alive
Female	325	11.2	17	12	233	0.55	0.78	68.952	95	NA	28/33	10.8/13.8	Alive
Female	82	12.6	36	29	253	0.82	0.96	84.864	72	Negative	38	17.3	Alive
Female	367	11.8	12	8	189	0.83	0.82	72.488	83	NA	28/33	10.8/13.8	Alive
Female	396	11	17	12	216	0.64	0.91	80.444	78	Negative	28	10.8	Alive
Female	44	11.6	34	13	50	8.3	0.8	70.72	83	Negative	51	28.3	Alive
Female	232	11.9	24	14	197	0.88	0.93	82.212	77	Negative	28	10.8	Alive
Male	110	12.6	40	21	48	5.82	1.16	102.544	78	Negative	20	6.9	Alive
Male	229	14.4	NA	10	192	NA	1.02	90.168	89	NA	6.0/11.0	2.8/3.9	Alive
Male	65	12.4	73	105	236	1.21	1.12	99.008	77	Negative	49	26.4	Alive
Male	221	14	42	33	521	0.38	1.41	124.644	64	NA	6/11.0	2.8/3.9	Alive
Female	145	11	NA	NA	165	NA	0.86	76.024	76	NA	38/43	17.3/21.2	Alive
Male	154	7.2	88	13	43	22.14	1.33	117.572	64	Negative	48	25.5	Alive
Male	334	11.3	20	8	586	0.49	2.19	193.596	35	Negative	34	14.4	Alive
Male	135	10	45	12	160	2.84	0.8	70.72	117	NA	38/43	17.3/21.2	Alive
Male	258	13.7	33	50	205	1.07	1.31	115.804	62	Negative	16	5.5	Alive
Male	275	14.2	65	77	267	0.8	0.92	81.328	103	NA	6/11.0	2.8/3.9	Alive
Male	317	11.5	86	145	222	0.23	0.59	52.156	NA	Negative	28	10.8	Alive
Male	74	12.6	73	90	176	1.49	0.9	79.56	103	Negative	44	22	Alive
Male	155	12	24	12	218	1.88	1.01	89.284	80	Negative	38	17.3	Alive
Female	153	10.9	31	20	169	0.49	0.63	55.692	NA	NA			Alive
Female	566	10.9	33	31	NA	NA	0.75	66.3	93	NA			Alive
Male	113	17.3	112	40	137	4.91	1.23	108.732	70	Negative	10	3.7	Alive
Male	39	10.3	23	14	73	3.62	1.2	106.08	70	Negative	51	28.3	Alive
Male	460	14.1	44	16	233	2.03	0.9	79.56	98	Negative	12	4.2	Death
Male	110	8.9	140	37	69	15.01	0.76	67.184	118	Negative	48	25.5	Death
Male	43	9.9	19	16	183	1.22	1.32	116.688	62	Negative	67	44	Death
Female	457	NA	NA	NA	NA	NA	NA	NA	NA	Negative			Alive
Male	1138	14.7	NA	NA	300	NA	1	88.4	91	Negative			Alive
Male	193	12.6	19	11	225	0.99	1.18	104.312	73	NA	20/25	6.9/9.2	LFU
Female	234	11.9	23	13	190	1.41	0.96	84.864	68	NA	28/33	10.8/13.8	Alive
Female	554	11.7	NA	12	NA	NA	0.73	64.532	92	Negative			Alive
Female	342	11.9	47	9	206	2.81	1.08	95.472	61	NA	34/39	14.4/18	Alive
Male	75	10.2	69	39	158	3.22	0.93	82.212	93	Negative	56	33	Alive
Female	196	8.2	44	12	176	2.74	6.47	571.948	8	Negative	80	56.6	Alive
Female	487	11.1	22	12	199	1.72	1.02	90.168	60	NA	46/51	23.7/28.3	Alive
Female	196	8.9	25	14	259	0.95	1.05	92.82	63	NA	48/53	25.5/30.1	Alive
Female	123	11.5	27	7	NA	NA	0.66	58.344	113	NA			Alive
Female	230	8.6	NA	8	NA	NA	0.85	75.14	81	Negative			Alive
Male	387	13.7	16	15	NA	NA	1.3	114.92	63	Negative			Alive
Male	215	11.2	28	12	141	2.58	0.94	83.096	92	NA	34/39	14.4/18	Alive
Male	651	9.3	NA	8	647	NA	1.58	139.672	46	Negative			Alive
Female	313	11.1	24	15	273	0.79	0.81	71.604	86	NA	28/33	10.3/13.8	Alive
Female	293	11.1	15	11	209	0.65	0.84	74.256	85	NA	28/33	10.8/13.8	Alive
Female	288	12.4	41	28	199	2.02	0.92	81.328	68	Negative	34	14.4	Alive
Male	639	NA	NA	NA	NA	NA	0.96	84.864	84	NA			Alive
Male	147	14.5	73	36	91	5.88	1.26	111.384	66	Negative	10	3.7	Alive
Female	21	8	18	10	154	1.18	0.69	60.996	105	Negative	67	44	Alive
Female	339	11.7	20	8	216	1.17	1.03	91.052	64	Negative	28	10.8	Alive
Female	774	10.3	NA	14	268	NA	0.6	53.04	NA	NA			Alive
Male	619	15.7	22	17		NA	1.11	98.124	79	NA			Alive
Male	244	17.4	27	19	147	2.53	1.19	105.196	66	Negative	24	8.7	Alive
Male	19	13.1	49	42	43	8.97	0.77	68.068	113	Negative	51	28.3	Alive
Male	298	14.2	21	12	281	1.1	1.01	89.284	83	Negative	18	6.2	Alive
Female	245	7.3	23	11	241	0.75	0.63	55.692	121	NA	44/49	22/26.4	Alive
Male	195	13.4	NA	10	212	NA	1.21	106.964	70	Negative			Alive
Male	236	15.6	168	130	351	1.85	1.26	111.384	66	Negative	12	4.2	Alive
Female	235	8.4	15	10	349	0.3	0.75	66.3	103	Negative	44	22	Alive
Female	301	10.5	20	13	257	0.71	0.9	79.56	77	NA	28/33	10.8/13.8	Alive
Female	269	12.4	14	8	NA	NA	0.79	69.836	91	NA			Alive
Male	209	13.3	28	13	129	3.25	1.09	96.356	75	Negative	28	10.8	Alive
Male	320	14.2	NA	58	NA	NA	1.04	91.936	83	NA			Alive
Female	53	10.1	56	23	285	1.6	0.76	67.184	90	Negative	56	33	Alive
Female	46	11.8	48	30	NA	NA	0.87	76.908	76	Negative			Alive
Male	50	12.8	34	36	51	3.78	1.06	93.704	85	Negative	38	17.3	Death
Male	302	12.2	22	13	142	1.38	0.98	86.632	94	Negative	16	5.5	Alive
Male	65	9.9	71	27	15	58.3	0.9	79.56	90	Negative	66	43	Alive
Male	408	13.3	23	33	NA	NA	1	88.4	87	NA			Alive
Male	220	8.3	34	14	248	1.28	1.47	129.948	58	NA	50/55	27.3/32.1	Alive
Female	106	11.3	NA	8	NA	NA	0.96	84.864	72	Negative			Alive
Male	232	13.6	70	97	145	2.25	1.2	106.08	69	Negative	22	7.8	Alive
Female	357	7.6	NA	19	137	NA	1.2	106.08	55	Negative			Alive
Male	19	12.6	63	59	72	6.04	1.06	93.704	78	Negative	51	28.3	LFU
Female	368	12.2	NA	15		NA	0.79	69.836	90	Negative			Alive
Female	311	12.1	21	12	299	0.71	0.89	78.676	77	Negative	16	5.5	Alive
Female	2	5.1	32	11	271	0.21	0.41	36.244	NA	NA	67/72	44/49	Death
Female	42	9.4	29	13	189	1.57	0.82	72.488	83	Negative	73	50	Alive
Female	698	11.4	20	12	229	0.71	0.8	70.72	91	Negative	22	7.8	Alive
Male	65	13.6	51	8	274	2.5	1.34	118.456	63	Negative	44	22	Alive

Female	130	10.6	30	15	150	2.69	0.8	70.72	80	Negative		50	27.3	Alive
Male	123	10	124	55	463	1.3	1.58	139.672	53	Negative		38	17.3	LFU
Female	220	11.5	76	29	253	1.9	0.8	70.72	87	Negative		34	14.4	Alive
Female	49	8.7	15	23	149	1.09	0.85	75.14	75	Negative		79	55.7	Alive
Female	285	12.4	NA	11	NA	NA	0.89	78.676	80	NA				Alive
Male	269	13.1	54	47	206	1.49	0.7	61.88	133	Negative		22	7.8	LFU
Male	891	8.8	43	14	227	0.1	0.56	49.504	NA	Negative				Alive
Male	132	14.3	19	9	150	1.35	0.92	81.328	101	NA	10/15.0	3.7/5.1		Alive
Male	332	17.6	21	25	163	1.13	1.19	105.196	71	NA	06/11.0	2.8/3.9		Alive
Female	317	8	85	54	NA	NA	NA	NA	NA	NA				Alive
Female	641	9.8	18	NA	NA	NA	0.65	57.46	120	Negative				Alive
Female	152	10.9	48	36	255	1.07	0.9	79.56	76	Positive		37	16.5	Alive
Male	340	13.1	NA	14		NA	1.41	124.644	56	Negative				LFU
Male	406	8.3	24	7	152	2.45	1.07	94.588	81	Negative		50	27.3	Alive
Female	211	8.6	27	22	258	0.94	1.39	122.876	44	Negative		50	27.3	LFU
Male	257	12	36	12	285	0.4	0.6	53.04	NA	Negative				Alive
Female	26	11	30	10	216	1.58	0.95	83.98	71	Negative		57	34	LFU
Female	284	8	63	19	255	2.21	1.14	100.776	56	NA	56/61	33/38		Alive
Male	266	12.4	27	17	NA	NA	1.09	96.356	75	Negative				Alive
Female	210	11.1	16	9	NA	NA	0.86	76.024	81	Negative				Alive
Male	146	NA	30	26	287	0.84	1.02	90.168	86	Negative				Alive
Female	403	10.8	34	25	440	0.17	NA	NA	NA	NA				LFU
Male	236	16.5	26	30	210	0.63	1.26	111.384	72	Negative		6	2.8	Alive
Female	196	8.7	30	17	197	1.63	0.79	69.836	84	NA	54/59	31.1/36		Alive
Female	403	7.5	79	77	196	1.7	0.85	75.14	80	NA	50/55	27.3/32.1		Alive
Female	330	10.3	16	10	203	0.72	0.96	84.864	73	Negative		28	10.8	Alive
Female	331	11.3	20	18	238	0.89	0.81	71.604	81	NA	28/33	10.8/13.8		Death
Female	313	12.5	47	17	NA	NA	0.96	84.864	70	Negative				Alive
Female	92	11.4	12	8	184	0.67	0.76	67.184	96	NA	50/55	27.3/32.1		LFU
Female	138	13.2	21	10	215	1.14	1.07	94.588	61	Negative		20	6.9	Death
Male	449	13.4	17	13	464	0.68	1.05	92.82	75	Negative		43	21.2	LFU
Male	118	15.8	9	19	258	0.26	1.04	91.936	87	NA	10/15.0	3.7/5.1		Alive
Female	89	10.7	16	11	NA	NA	0.64	56.576	121	Negative				Alive
Male	509	13.5	NA	NA	NA	NA	1.21	106.964	68	NA				LFU
Male	309	15.1	45	47	237	1	1.48	130.832	57	Negative		12	4.2	Alive
Male	528	12.7	NA	43	NA	NA	1.06	93.704	81	Negative				Alive
Male	7	9.3	70	25	418	0.37	0.49	43.316	NA	NA				Alive
Female	238	9.5	16	11	280	0.57	0.82	72.488	85	Negative		44	22	LFU
Male	153	15.7	502	150	112	16.47	1.24	109.616	67	Negative		10	3.7	Alive
Male	509	10.5	70	34	94	5.75	1.1	97.24	77	Negative		22	7.8	Alive
Male	157	14.1	34	11	170	3.86	0.9	79.56	90	Negative		10	3.7	Alive
Male	355	14.2	20	24	229	0.66	1.02	90.168	87	Negative		6	2.8	Alive
Male	106	9.9	24	15	491	0.53	1.08	95.472	80	NA	48/53	25.5/30.1		Alive
Male	159	15.4	NA	NA	281	NA	0.85	75.14	105	Negative				Alive
Male	353	13.7	54	53	229	1.52	0.81	71.604	109	Negative		22	7.8	Alive
Male	299	12.8	23	27	253	0.66	1.37	121.108	62	Negative		16	5.5	Alive
Male	131	15.7	37	12	236	2.08	1.48	130.832	54	Negative		22	7.8	LFU
Female	238	13.3	18	10	167	1.16	0.68	60.112	105	Negative		16	5.5	Alive
Male	283	13.7	119	198	98	2.42	1.13	99.892	82	NA	22/27	7.8/10.2		Alive
Male	72	11.5	35	10	163	2.78	0.95	83.98	93	Negative		56	33	LFU
Male	14	6.4	83	13	246	3.09	1.04	91.936	87	Negative		73	50	LFU
Male	2	10.5	54	26	161	1.32	1.12	99.008	89	Negative		51	28.3	Death
Male	135	11.6	17	10	244	0.79	1.23	108.732	71	Negative		32	13.1	Alive
Female	114	12.2	36	27	380	1	0.94	83.096	66	NA	32/37	13.1/16.5		LFU
Male	84	10.9	22	7	399	0.67	1.03	91.052	89	Negative		50	27.3	Alive
Male	86	9.9	26	10	258	1.75	1.37	121.108	57	Negative		90	65.1	LFU
Male	147	12.3	18	21	78	1.61	1.02	90.168	90	Negative		26	9.7	Alive
Female	332	14.9	52	70	257	0.94	1.31	115.804	48	Negative		12	4.2	Alive
Female	249	10.8	NA	32		NA	0.85	75.14	82	Negative				LFU
Male	17	14.8	50	31	215	1.67	0.95	83.98	93	Negative		35	15.1	Alive
Male	132	14.1	20	11	202	1.52	1.04	91.936	80	NA	28/33	10.8/13.8		Alive
Male	378	11.9	NA	30	242	NA	0.64	56.576	NA	Negative				Alive
Female	1166	11.4	13	10		NA	0.74	65.416	99	NA				Alive
Female	33	9.8	NA	NA	166	NA	NA	NA	NA	Negative				LFU
Male	76	11.1	39	18	312	1.24	1.25	110.5	67	Negative		50	27.3	Alive
Female	325	12.7	24	18	204	0.83	0.97	85.748	72	Negative		16	5.5	Alive
Female	444	8.1	36	12	186	1.79	0.9	79.56	77	Negative		50	27.3	Alive
Female	36	5.9	26	12	257	1.23	0.88	77.792	75	Negative		67	44	LFU
Female	540	8.1	36	15	175	2.18	1.21	106.964	52	NA	50/55	27.3/32.1		Alive
Female	774	11.3	10	12	99	1.22	0.69	60.996	99	NA	22/27	7.8/10.2		Alive
Female	372	12.3	NA	17	247	NA	0.7	61.88	104	Negative				Alive
Male	257	12.6	29	28		NA	1.01	89.284	91	Negative				LFU
Female	238	6.9	16	5	258	1.22	0.85	75.14	77	Negative		44	22	Alive
Male	259	14.3	NA	18	205	NA	1.23	108.732	64	Negative				Alive
Male	126	10.6	16	6	278	0.99	1.11	98.124	77	Negative		32	13.1	Alive
Male	41	8.2	56	14	143	5.13	1.33	117.572	61	Negative		67	44	Alive
Female	38	10.4	45	31	341	1	1.45	128.18	42	Negative		57	34	LFU
Female	28	9.2	54	28	263	1.36	0.9	79.56	76	Negative		67	44	Death
Female	198	11.4	NA	30	NA	NA	0.7	61.88	102	NA				Alive
Male	143	8.3	25	20	228	0.39	NA	NA	NA	NA				LFU
Female	778	12.5	NA	NA	NA	NA	NA	NA	NA	Negative				Alive
Male	306	13.7	25	20	212	1.5	1.07	94.588	76	Negative		40	18.8	Alive
Male	51	9.5	51	29	256	1.63	1.34	118.456	62	Negative		72	49	LFU
Male	425	14.2	25	21	244	0.98	1.17	103.428	72	Negative		6	2.8	Alive
Male	581	15.4	40	62	188	0.97	0.99	87.516	91	NA	0/5	1.8/2.6		Alive

Male	46	10.9	17	11	300	1.14	1.02	90.168	77	Negative	78	54.7	LFU
Female	308	13.1	20	15	96	2.74	1.03	91.052	60	NA	34/39	14.4/18	Alive
Male	170	12.9	21	9	274	1.15	1.09	96.356	78	Negative	20	6.9	LFU
Male	290	14.9	144	164	242	2.23	0.91	80.444	95	NA	12.0/17	4.2/5.8	Alive
Male	163	15.4	17	17	142	1.22	1.1	97.24	78	Negative	10	3.7	LFU
Male	218	11.4	38	9	169	1.2	0.68	60.112	NA	NA			Alive
Female	317	11.4	22	9	200	1.58	1.06	93.704	60	Negative	34	14.4	LFU
Male	275	10.6	57	15	NA	NA	0.98	86.632	87	Negative			LFU
Male	108	10.8	18	10	333	0.89	1.19	105.196	68	Negative	44	22	Alive
Female	233	9.3	20	10	281	0.5	1.35	119.34	52	Negative	50	27.3	Alive
Female	332	14.1	NA	16	NA	NA	0.92	81.328	69	Negative			Alive
Male	917	14.2	NA	22	NA	NA	1.1	97.24	80	NA			Alive
Male	49	11.8	29	51	NA	NA	0.86	76.024	107	Negative			Alive
Male	333	16.4	NA	22	NA	NA	1.2	106.08	75	Negative			Alive
Male	55	10.8	128	46	103	6.23	0.77	68.068	123	Negative	50	27.3	Death
Female	172	11.3	23	21	192	0.84	0.77	68.068	92	Negative	32	13.1	Alive
Female	756	11.2	NA	NA	NA	NA	NA	NA	NA	NA			LFU
Male	99	13.9	23	22	226	0.95	0.92	81.328	95	NA	38/43	17.3/21.2	LFU
Female	246	12	17	9	80	2.13	1.05	92.82	65	NA	22/27	7.8/10.2	Alive
Male	450	14.8	31	39	180	1.02	1.17	103.428	75	NA	06/11.0	2.8/3.9	Alive
Female	209	13.3	23	21	6	38.48	0.61	53.924	112	Negative	16	5.5	LFU
Male	57	10.8	NA	11	NA	NA	0.94	83.096	91	Negative			Alive
Male	38	10.1	19	9	276	1.03	1.12	99.008	75	Negative	51	28.3	Alive
Male	29	13	26	37	312	0.6	0.92	81.328	95	Negative	39	18	Alive
Male	174	13.8	13	15	199	0.91	0.82	72.488	104	Negative	32	13.1	Alive
Female	178	9.2	30	15	NA	NA	0.81	71.604	85	NA			Alive
Female	61	3.7	26	10	42	8.81	0.95	83.98	68	Negative	66	43	Alive
Female	336	12.5	NA	11	NA	NA	0.77	68.068	91	Negative			Alive
Female	215	11	28	19	164	1.65	0.77	68.068	87	Negative	34	14.4	LFU
Male	296	14.2	NA	15	NA	NA	1.23	108.732	71	Negative			Alive
Female	303	13.7	NA	34	NA	NA	0.86	76.024	82	NA			Alive
Female	341	12.7	NA	10		NA	0.81	71.604	82	Negative			Alive
Female	64	9.4	32	15	287	1.09	0.96	84.864	69	Negative	66	43	Alive
Female	36	12.3	64	52	175	2.43	1.87	165.308	31	Negative	51	28.3	Alive
Female	312	12.8	26	13	144	1.8	1.21	106.964	54	NA	28/33	10.8/13.8	Alive
Female	263	10.3	17	11	161	1.27	0.9	79.56	74	Negative	28	10.8	LFU
Female	844	13.4	16	11	NA	NA	0.95	83.98	71	Negative			LFU
Male	22	10.6	60	20	169	4.53	1.09	96.356	74	Negative	63	40	LFU
Male	289	10.8	22	16	259	1.38	1.08	95.472	73	Negative	55	32.1	Alive
Male	687	14.4	NA	12	NA	NA	0.88	77.792	102	Negative			Alive
Male	579	15.3	NA	12	206	NA	1.13	99.892	76	Negative			Alive
Male	42	12.8	34	44	188	1.06	1.15	101.66	75	Negative	39	18	Death
Male	177	12.8	31	12	NA	NA	0.87	76.908	117	Negative			LFU
Male	494	10.1	19	20	103	1.73	1.08	95.472	80	Negative	34	14.4	Alive
Male	46	16.6	611	297	100	17.02	1.22	107.848	67	Negative	29	11.3	LFU
Female	162	11.1	32	14	316	0.87	0.77	68.068	92	Negative	32	13.1	Alive
Male	46	12.6	30	22	128	2.15	1.12	99.008	76	Negative	45	22.9	LFU
Female	376	11.9	19	12	214	0.97	0.97	85.748	68	NA	28/33	10.8/13.8	Alive
Female	361	10.2	18	12	287	0.62	0.8	70.72	87	NA	28/33	10.8/13.8	Alive
Male	182	10	90	47	320	2.22	1	88.4	83	Negative	50	27.3	LFU
Male	60	16.5	39	29	248	1.64	1.18	104.312	68	NA	46/51	23.7/28.3	Death
Female	269	12.2	NA	25	NA	NA	0.82	72.488	86	NA			Alive
Female	111	10.2	17	9	NA	NA	0.66	58.344	118	NA			Alive
Female	493	11	NA	NA	NA	NA	NA	NA	NA	NA			LFU
Female	443	12	NA	10	NA	NA	0.75	66.3	97	NA			Alive
Male	384	7.4	58	17	288	1.17	1.05	92.82	92	Negative	44	22	LFU
Female	167	10	25	18	238	0.67	0.75	66.3	99	Negative	32	13.1	Alive
Male	192	13.1	46	64	99	2.03	1.19	105.196	74	NA	26/31	9.7/12.5	Alive
Female	272	12.3	12	19	NA	NA	0.98	86.632	69	Negative			Alive
Female	1646	9.6	121	72	316	0.27	0.49	43.316	NA	Negative			LFU
Female	253	12.1	78	40	310	1.95	0.83	73.372	78	Negative	22	7.8	Alive
Female	225	12	13	23	238	0.56	0.81	71.604	80	Negative	16	5.5	Alive
Female	778	12.4	NA	NA	NA	NA	0.8	70.72	90	NA			Alive
Female	318	12.2	26	15	233	1.01	0.8	70.72	87	NA	16/21	5.5/7.5	Alive
Male	202	12.8	16	7	185	1.47	1.04	91.936	82	Negative	22	7.8	Alive
Male	515	16.2	NA	29	NA	NA	1.13	99.892	83	Negative			Alive
Male	56	12.3	108	116	120	3.84	1.24	109.616	67	Negative	38	17.3	Alive
Male	90	17.1	46	70	163	1.21	0.94	83.096	97	Negative	28	10.8	Alive
Female	230	10.2	20	9	487	0.62	1.06	93.704	60	Negative	34	14.4	Alive
Male	31	9.5	45	44	165	2.14	1.02	90.168	82	Negative	85	61	Alive
Female	127	8.5	18	8	NA	NA	0.79	69.836	84	Negative			Alive
Male	260	5.6	114	68	142	3.5	1.39	122.876	61	Negative	44	22	Alive
Female	351	12.3	22	17	276	0.68	0.74	65.416	95	NA	16/21	5.5/7.4	Alive
Male	318	13.9	179	13	207	10.79	1.36	120.224	60	Negative	16	5.5	Alive
Male	421	15	NA	NA	NA	NA	1.08	95.472	74	NA			Alive
Male	447	14.7	26	16	NA	NA	1.02	90.168	85	NA			Alive
Female	312	11.4	18	13	199	1.15	0.9	79.56	72	Negative	28	10.8	Alive
Female	738	12.2	16	8	201	0.87	0.81	71.604	88	NA	10/15.0	3.7/5.1	LFU
Male	763	15.3	16	21	NA	NA	1.2	106.08	73	NA			Alive
Female	360	12.3	18	21	NA	NA	0.78	68.952	97	NA			Alive
Male	391	NA	NA	11	NA	NA	0.71	62.764	NA	NA			Alive
Male	103	11.2	NA	14	NA	NA	0.79	69.836	122	Negative	32	13.1	Alive
Female	346	12.2	18	10	NA	NA	0.72	63.648	102	NA	16	5.5	Alive
Male	447	12.2	16	15	170	1.26	1.25	110.5	64	Negative	28	10.8	Alive